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COURSE AND RATE OF REGENERATION OF MOTOR FIBERS FOLLOWING LESIONS OF THE RADIAL NERVE

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THE OBJECT of this paper is to record and to discuss the significance of observations on the course and rate of regeneration of motor fibers following complete interruption of conduction in the radial nerve due to gunshot wounds, simple fractures of the humerus, penetrating injuries and lacerations. The results of an investigation of simple compression injuries of this nerve have already been described (Sunderland [1]).

Detailed observations on motor recovery have been reported by Stopford [2] and by Seddon, Medawar and Smith.[3] Reference will be made to the results of their studies in the appropriate sections of the text.

In the present investigation of a series of 63 lesions of the radial nerve particular attention was paid to the following points:

1. End results
2. Course of spontaneous regeneration and the regeneration following suture
3. Pathologic features of the lesion, as deduced from a study of the course of regeneration
4. Selection of cases suitable for investigation of the rate of regeneration of peripheral nerves in man
5. Rate of regeneration, which was estimated over different segments of the nerve in order to determine whether regeneration progresses at a uniform rate or otherwise

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1. Sunderland, S.: Traumatic Injuries of Peripheral Nerves: I. Simple Compression Injuries of the Radial Nerve, Brain **68**:56-72, 1945.

2. Stopford, J. S. B.: The Results of Secondary Suture of Peripheral Nerves, Brain **43**:1-25, 1920.

3. Seddon, H. J.; Medawar, P. B., and Smith, H.: Rate of Regeneration of Peripheral Nerves in Man, J. Physiol. **102**:191-215, 1943.

6. Composition and duration of the interval between the time of the injury and the onset of recovery and the influence of this interval on the course of regeneration subsequent to the latter

7. Maximal latent period subsequent to the injury after which spontaneous regeneration may still occur and proceed to completion.

MATERIAL AND METHOD OF INVESTIGATION

The observations are based on a group of 63 cases of lesions of the radial nerve occurring in a series of 301 consecutive cases of peripheral nerve injuries which were personally studied over the period of 1941 to 1945 at the One-Hundred and Fifteenth Australian General Hospital and the Repatriation Clinic, Melbourne, Australia. The case histories and the end results in these 63 cases are to be reported in considerable detail elsewhere. Only 31 of these cases were suitable for the purposes of the present study, which demanded that interruption of conduction in the nerve should be complete when the patient first came under observation and that examinations should subsequently be made at regular and frequent intervals in order to obtain information which would enable one to ascertain, with reasonable accuracy, the time and order of motor recovery in individual muscles.

Throughout the text cases have been referred to by serial number only (personal series), and reference should be made to table 2 for information concerning the injury responsible for each nerve lesion and the level of the lesion above the lateral epicondyle of the humerus.

To make possible a comparison of the observations and results in this series with those obtained by other investigators, it is proposed, before proceeding to the discussion, to define and specify the exact meaning ascribed to certain terms employed in this report.

Initial Delay.—The interval between the injury and the time when regenerating axons enter the distal segment is termed the initial delay.

Latent Period.—The interval between the injury and the onset of recovery is termed the latent period.

Infection and Scarring.—An attempt was made in each case to assess the degree of infection and local scarring about the nerve in order to determine the influence of these factors on the course of regeneration. This was obviously difficult, and only the simplest classification into "significant" and "insignificant" was attempted.

The degree of infection was assessed on the basis of general symptoms, culture of material from the wound, presence or absence of osteomyelitis, period during which the wound discharged, time taken for the wound to heal and extent of residual scarring.

The degree of scarring was estimated on the extent of injury to soft tissue and on the area and character of the residual scar and whether this was adherent, free, depressed or otherwise.

Motor Recovery.—In studying motor recovery particular attention was directed to the onset of contraction in the brachioradialis, extensor carpi radialis longus, extensor digitorum communis, extensor carpi ulnaris, abductor pollicis longus and extensor pollicis longus muscles. No attempt was made when examining muscular function to separate the respective muscles of the extensor carpi radialis group, the abductor pollicis longus from the extensor pollicis brevis or the segment of the extensor digitorum communis to the index finger from the extensor

indicis proprius. The members of each group have substantially the same actions and are so closely associated anatomically that it is often impossible to decide with absolute certainty by palpation when one is contracting and the other is not.

A study of the metric and nonmetric features of the motor branches of the radial nerve in 20 specimens revealed that the shortest distance to the extensor carpi radialis longus as measured from a fixed point along the nerve and its branches was invariably shorter than that to the extensor carpi radialis brevis. The first contractions in this combined mass could therefore be attributed to the former provided the regenerating axons to each muscle grow at the same rate and commence to do so at the same time.

In no instance were the shortest fibers to the extensor indicis proprius shorter than those to the extensor digitorum communis. In 4 specimens the extensor digiti quinti proprius preceded the extensor digitorum communis in the order of innervation, though in only 2 of these was the difference between their lengths significant. Consequently, the extensor digitorum communis may, as a rule, be expected to recover before the other two muscles, and its action should not be attributed to them.

In every specimen the distance to the abductor pollicis longus was shorter than that to the extensor pollicis brevis, and therefore in cases of uncomplicated recovery the first signs of returning function should be attributed to the former.

Palpable contraction of the muscle, or movement which was undoubtedly attributable to its action alone, was the criterion adopted for detecting returning function, and in this connection due regard was paid to the possibility of transmitted contraction and trick movements. One source of error, however, remains. It has been found that electrical stimulation of a nerve at operation may produce a response in a muscle before the appearance of voluntary contraction. This indicates that reinnervation of a muscle and its ability to contract voluntarily do not necessarily return simultaneously. Case 231, in the group of gunshot wounds associated with fractures of the humerus, will illustrate this point. The radial nerve, which had originally been reported as completely severed, was explored twenty-six weeks after the injury, when infection had subsided. It was exposed in the middle and distal thirds of the arm and appeared normal in every respect. Direct and strong stimulation of the nerve resulted in a flicker of contraction in some of the fibers of the brachioradialis. The nerve was not disturbed. Contraction to clinical examination did not appear in the brachioradialis until 40 weeks after the injury, that is, 14 weeks after it was obtained by direct and strong electrical stimulation of the nerve at operation.

A possible explanation of this phenomenon is that functionally immature fibers were stimulated and that the ability to contract voluntarily depends on the presence of functionally mature fibers. In this study it was the growth of the latter that was under investigation, and since it is impossible to evaluate the aforementioned phenomenon, which is probably operating in all muscles, though not necessarily to the same degree, its influence on the onset of recovery as detected by clinical examination has, perforce, been disregarded.

In order to detect the earliest signs of recovery, patients were examined at weekly intervals until all muscles were contracting, from which time onward the examinations were conducted at monthly, then at three monthly and, finally, at six monthly intervals. When weekly examinations were not possible and the first appearance of recovery could not therefore be limited accurately to a specific week, the last date when the muscle was known to be still paralyzed and the date when recovery was first detected were given in the tables.

Treatment.—Treatment in all cases consisted of daily massage, heat therapy, exercises and supervised and controlled splinting. Electrotherapy was not employed.

All muscles were splinted in a relaxed condition until contraction appeared. This point is mentioned specifically, because it is my experience that the onset of recovery may be delayed in unsupported muscles, whereas there is evidence to suggest that electrotherapy hastens the return of function. Consequently, since it would appear that the form of treatment affects to a certain extent the onset and progress of recovery, it is considered advisable to specify the treatment employed in any study of rates of regeneration.

END RESULTS

A brief résumé of the end results is necessary for an appreciation of the clinical basis of this investigation. They have been summarized in table 1.

TABLE 1.—*End Results in Sixty-Two Cases of Lesions of the Radial Nerve* *

Causative Injury	Spontaneous Regeneration	Combination of Spontaneous Regeneration and Tendon Transplant	Exploration			
			Irreparable Damage	Suture	Suture Under Tension	No Surgical Treatment Indicated
Simple compression	8	..	..	..	..	..
Tourniquet	2	..	..	..	..	..
Simple fracture of humerus	4	..	..	..	..	1
Laceration or penetrating injury	1	..	1	3	..	..
Gunshot wound	12	..	..	1	1	..
Gunshot wound and fracture of humerus	16	2	7	1	1	1
Total	43	2	8	5	2	2

* The records are incomplete for 1 additional case.

In general, patients with peripheral nerve injuries sustained in the Middle East campaigns were repatriated to Australia as soon as possible. Such patients were retained in the Middle East until suitable transport was available, and this delay, together with the time taken on the voyage home, lengthened considerably the interval between the date of the injury and the time when the patient came under observation in a base hospital in Australia. The late onset of spontaneous regeneration in a large proportion of these patients encouraged a conservative attitude in the treatment of those patients in whom the state of the nerve was not known.

Spontaneous regeneration proceeded either to completion or to a degree which contraindicated exploration of the nerve in 45 of the 62 cases investigated—in 1 other case the patient was transferred to another state before the onset of recovery. Of the 17 cases in which exploration was made, the nerve was irreparably damaged in 8, and in 2 cases it was sutured under tension. There was no recovery in these 2 cases,

forty-three and fifty weeks, respectively, after the suture. In 5 cases the nerves were sutured under favorable conditions; and of these, recovery was satisfactory in 4 and was proceeding satisfactorily in the fifth at the time of writing. In the remaining 2 cases the nerve was left undisturbed. In 1 of these 2 cases exploration of the nerve had been undertaken because of a statement in the field notes that it had been severed, but when exposed the nerve appeared normal. In the second (case 65, described later) interruption of conduction was still complete six months after the injury, at which time it was considered that spontaneous regeneration should have made its appearance if it were going to do so. The condition of the nerve is described in the section devoted to the pathologic study. Spontaneous regeneration appeared thirteen to forty weeks after neurolysis and proceeded to a satisfactory conclusion.

The observations may be summarized as follows:

1. The majority of lesions of the radial nerve recovered spontaneously and did not require exploration. This is in accord with the experience of others and accounts for the beneficial results often incorrectly attributed to neurolysis when this has been performed prematurely.

2. Conditions were favorable for suture in less than one-half the cases in which the condition of the nerve was not known but in which exploration was ultimately indicated.

3. The majority of the irreparable lesions were due to gunshot injuries accompanied by fracture of the humerus.

COURSE OF SPONTANEOUS REGENERATION AND REGENERATION FOLLOWING SUTURE

Provided regeneration commences simultaneously and advances at a uniform rate in all the axons and that, after their entry into each muscle, the time taken for the nerve fibers to reestablish functional relationships is approximately the same, it may reasonably be expected that the various muscles should commence to contract in an order which is determined by the length of the fibers composing their motor branches from the site of injury to the muscle. The order of motor recovery is usually, but not necessarily, that in which the motor branches leave the nerve, since the first branch to a muscle may not be the shortest route to it.

The actual lengths of the motor fibers to the particular muscle they innervate, as measured along the nerve and its branches from a fixed point, were determined by dissection. According to these measurements, the test muscles are customarily innervated in the order of the

brachioradialis, the extensor carpi radialis longus, the extensor digitorum communis and extensor carpi ulnaris, the abductor pollicis longus and, finally, the extensor pollicis longus. In general the muscles were found to recover in this order. Departures from this serial reinnervation took one of three forms:

1. Contraction in two neighboring muscles appeared simultaneously. This could be attributed either to the fact that the distances to be covered by the regenerating axons in each case were equivalent or approximately so or to the fact that the difference between those distances was so small that the onset of recovery must have occurred in both muscles within the time interval between examinations.

2. Contraction appeared almost simultaneously over the entire pattern. This usually occurred shortly after the injury was sustained and could be explained only on the basis that the distal segment had not undergone wallerian degeneration and that after a period of quiescence the entire pattern reawakened to activity. This form of recovery is characteristic of simple compression injuries.

3. There was a variation in the order of recovery of the muscle. Four factors may be responsible for this variation, and these may operate singly or in combination.

(*a*) The axons to the muscle taking abnormal precedence in the order of recovery may have a shorter distance to travel than those to muscles customarily recovering before it. The possible variations in the order of innervation of individual muscles (estimated on the basis of the shortest distances to each muscle from a fixed point on the radial nerve) have been reported separately. It is not uncommon, for example, for the extensor carpi ulnaris to be innervated before the extensor digitorum communis—in this series the former recovered before the latter in 5 of the 31 cases. Though Stopford [2] also recorded this variation, Seddon, Medawar and Smith [3] did not observe it and erroneously concluded that on anatomic grounds it could not occur.

(*b*) Axons for more proximally innervated muscles may be delayed at the site of injury for a period longer than those destined for more distally supplied muscles. The difference in the onset of regeneration at the site of injury must be sufficiently great to enable the latter to be reinnervated before the former.

(*c*) The site of injury may be such that the first, or higher, branches to a muscle, on which its early recovery depends, are directly involved, either severely or irreparably. Reinnervation of this muscle is then dependent on more distal branches, when such are present, and this involves a longer route to the muscle. By the time regenerating axons have covered this longer route muscles supplied by shorter

branches arising at higher levels are contracting. This, it is believed, accounts for the unusual delay occasionally seen in the reinnervation of the brachioradialis after wounds involving the nerve in the furrow.[4]

(*d*) All axons may not be involved to the same degree. This was well illustrated in case 114, in which the nerve was injured 24 cm. above the level of the lateral epicondyle. The extensor carpi radialis longus was observed to contract nine weeks and the brachioradialis sixteen weeks after the injury. The recovery of the extensor carpi radialis longus nine weeks after the injury could not be explained on the basis of complete wallerian degeneration occurring in the fibers to that muscle with a subsequent axonal growth distally unless this occurred at a rate far greater than that revealed by any investigation. Furthermore, although in 3 of 20 specimens examined anatomically the fibers to the extensor carpi radialis longus and the brachioradialis muscle were approximately equal in length, in no case were the fibers to the former shorter than those to the latter.

The only adequate explanation for the early recovery of the extensor carpi radialis longus is that the fibers supplying it had suffered an injury of the type defined by Seddon[5] as neurapraxia. In the case of the brachioradialis and the remaining muscles the onset of recovery was consistent with regeneration having followed complete wallerian degeneration after a short initial delay at the site of the injury.

PATHOLOGIC STUDY

Observed Pathologic State.—Details relating to the wounds and the nature of the nerve injuries are to be provided in another paper. Only a brief account is necessary for the purposes of the present discussion.

In the following 3 cases the nerve was sutured, and the times of recovery for the individual muscles (table 2) date from the time of suture.

CASE 40.—There was complete severance of the nerve in the furrow, due to a gunshot injury. Secondary suture was done forty-four weeks later.

CASE 180.—There was complete severance of the nerve in the furrow, due to a bayonet injury. The nerve was sutured thirty-eight days later.

CASE 282.—There was almost complete severance of the nerve in the spiral groove due to injury from an ax. Primary suture was done.

In the remaining cases complete interruption of conduction was followed by spontaneous regeneration. In 22 cases the nerve was not seen. In the rest the

4. "Furrow" indicates the intermuscular furrow outlined between the brachialis muscle, medially, and the brachioradialis and extensor carpi radialis longus muscles, laterally.

5. Seddon, H. J.: A Classification of Nerve Injuries, Brit. M. J. **2**:237-239, 1942; Three Types of Nerve Injury, Brain **66**:238-288, 1943.

condition of the nerve was reported in the battle notes or at subsequent exploration, as follows:

CASE 65.—Simple comminuted fracture of the upper third of the shaft of the right humerus was present. The radial nerve was explored from the axilla to the spiral groove twenty-four weeks after the injury. It was adherent to the humerus at the site of fracture and was freed with difficulty. A small neuroma was situated just above the point where the nerve was firmly adherent to bone,

TABLE 2.—*Time and Order of Motor Recovery in Thirty-One Cases of Complete Interruption of Conduction of Radial Nerve*

Case No.	Causative Injury	Level of Injury Above Epicondyle, Cm.	Infection *	Scarring *	Return of Voluntary Contraction,† Weeks					
					BR.	E.C.R.L.	E.D.C.	E.C.U.	A.P.L.	E.P.L.
65	Simple fracture...	24.0	Nil	Nil	37-64	37-64	37-64	37-64	37-64	37-64
77	Simple fracture...	10.0	Nil	Nil	16	18	23	23	25	27
161	Simple fracture...	10.0	Nil	Nil	13	14	21	23	25	28
232	Simple fracture...	10.0	Nil	Nil	9	8.5	8.5	8.5	9	9
317	Simple fracture...	10.0	Nil	Nil	16	18	24	22	25	29
195	Laceration.....	15.0	Nil	Nil	11-14	11-14	18	19-23	19-23	19-23
114	Gunshot wound...	24.0	I	Nil	16	9	19	19	27	28
185	Gunshot wound...	12.0	Nil	Nil	14	16	22	24	26	30
244	Gunshot wound...	15.0	Nil	S	6	6	28	28	29-46	29-46
27	Gunshot wound...	12.5	Nil	Nil	Intact‡	3	13	19	13	21
64	Gunshot wound...	11.0	Nil	Nil	22-29	22	22-29	22-29	22-29	22-29
79	Gunshot wound...	10.0	Nil	Nil	4-18	4-18	21	26	28-30	28-30
203	Gunshot wound...	9.0	Nil	Nil	20	20	27	27	31	31
255	Gunshot wound...	2.0	I	S	8	8	18	18	20	26
264	Gunshot wound...	1.0	Nil	S	Intact	14	23	23	25	34
69	Gunshot wound...	Furrow	I	S	Intact	14-20	13	14-20	14-20	25
97	Gunshot wound...	Furrow	I	S	Intact	12	22	17	22-58	22-58
202	Gunshot wound...	Furrow	I	S	14	14	8	14	10	10
99	Gunshot wound + fracture.....	20.0	I	S	26-28	24	26-28	26-28	26-28	33
18	Gunshot wound + fracture.....	19.0	I	S	51-76	23-30	23-30	23-30	23-30	23-30
214	Gunshot wound + fracture.....	15.0	I	S	3	3	5	5	6	6
231	Gunshot wound + fracture.....	12.5	I	S	40	42	50	45	50	56
234	Gunshot wound + fracture.....	12.5	Nil	Nil	6	6	10-14	10-14	10-14	10-14
72	Gunshot wound + fracture.....	11.0	Nil	Nil	Intact‡	20	20-30	20-30	20-30	20-30
118	Gunshot wound + fracture.....	9.0	I	S	16	17-20	17-20	17-20	28	28
100	Gunshot wound + fracture.....	7.5	I	S	Intact	23	28-31	28-31	32-36	32-36
106	Gunshot wound + fracture.....	5.0	I	S	17	20	27	30	31	36
258	Gunshot wound + fracture.....	5.0	I	S	18	22	32	31	35	37
	Suture									
282	Laceration.....	12.5	Nil	Nil	22	27	37	36	40	45
180	Laceration.....	4.0	Nil	S	28	20	31	31	34	42
40	Gunshot wound...	5.0	I	S	Intact	20	34	35	40	40

* I and S indicate significant infection and scarring, respectively.

† In this table, BR. indicates brachioradialis; E.C.R.L., extensor carpi radialis longus; E.D.C., extensor digitorum communis; E.C.U., extensor carpi ulnaris; A.P.L., abductor pollicis longus, and E.P.L., extensor pollicis longus.

‡ The muscle was originally paralyzed but was contracting when I first examined it.

and a second neuroma was observed 2.5 cm. above this. Between the neuromas the nerve was much thinned out. Stimulation of the nerve immediately above and below the neuromas produced no response. Excision of the involved segment was demanded, but this would have necessitated the insertion of a graft; and, in the anticipation that the neurolysis might encourage regeneration, further repair

work on the nerve was abandoned. Spontaneous regeneration appeared 13 to 40 weeks later and proceeded to a satisfactory conclusion.

CASE 202.—The nerve was observed in the furrow and appeared normal.

CASE 203.—There were contusion and superficial laceration of the nerve in the furrow.

Case 231.—It was reported that the nerve was torn and a piece blown away. On the basis of this information, and since no contraction could be detected clinically, the nerve was explored twenty-six weeks after the injury. It was observed to be in continuity and appeared normal, and stimulation above the level of injury resulted in feeble contraction of the brachioradialis. The original report was obviously incorrect.

CASE 244.—The nerve was traumatized and hemorrhagic in the spiral groove but was not severed.

CASE 264.—The nerve was reported to be completely severed in the furrow. No repair was effected. The lesion appeared to be complete clinically. The subsequent progress of recovery, which terminated in complete restoration of function, suggested that the severed nerve seen was not the radial nerve.

Deduced Pathologic State.—An assessment of the nature of the nerve injury was attempted on the basis of the course of regeneration. In cases 18, 64, 65, 72, 79, 97, 100 and 195 there were insufficient data available to permit this.

The course of motor regeneration in cases 214, 232 and 234 closely resembled that following simple compression injuries of the radial nerve. In these 3 cases and in the group of cases of simple compression injury muscles innervated at different distances from the site of injury burst into activity simultaneously. The accumulated evidence, both clinical and experimental, supports the belief that the histopathologic changes leading to interruption of conduction in simple compression injuries must differ in some respects at least from the changes seen after a breach of continuity of the nerve fibers. These changes are reversible and apparently do not involve wallerian degeneration.

The observations in the 3 cases mentioned, however, differed from those in cases of simple compression injuries in certain important particulars:

(*a*) The length of the quiescent period was greater than that observed in any of the cases of simple compression injury. The present observations suggest that nerves may cease to conduct for 63 days and yet reawaken to activity without invoking any of the changes associated with wallerian degeneration and the regenerative process which follows it.

(*b*) In all 3 cases the superficial radial nerve was involved (in case 234 the dorsal cutaneous nerve of the forearm was independently divided). Sensation in the field of the superficial radial nerve was still defective sixty, seventy-three and forty-five weeks after the lesions,

which was long after motor recovery was complete. The occurrence and persistence of sensory defects are in contrast to the condition obtaining in cases of simple compression injuries, in which sensation is usually undisturbed. As has been pointed out, however (Sunderland [1]), sensory defects do appear with the more severe simple compression injuries, and when they are well established restoration of full motor function is considerably delayed. The present observations confirm this.

(*c*) Wasting persisted longer than with injuries due to simple compression. Estimation of wasting which could be definitely attributed to the lesion of the radial nerve was not possible in cases 232 and 234, owing to the presence of an associated lesion of the median nerve. In case 214 wasting, which could be attributed to the lesion of the nerve, was still present to the extent of 1.1 cm. above and 2 cm. below the lateral epicondyle sixty weeks after the injury. Wasting was observed in the cases of simple compression injury, but in no case did it persist for this length of time.

(*d*) Recovery of motor power was slow. In cases 232 and 234 there was an associated lesion of the median nerve. So far as could be ascertained in the presence of this complication, motor power was restored to normal thirty-one (case 232) and thirty-two (case 234) weeks after the injury. In case 214 the average dynamometric readings for the grip sixty weeks after the injury were 270 and 330 millimeters for the right and left hands, respectively (the patient was right handed). The slow recovery of power was a feature of these cases. On the other hand, rapid restoration to full power was a feature of the cases of simple compression injury.

These 3 cases present features which are implied in the terms "neurapraxia" and "axonotmesis," as defined by their originators.

The persistence of weakness, wasting and sensory defects for considerable periods after the injury indicated an intraneural disturbance of sufficient severity to result in peripheral degeneration followed by delayed or incomplete regeneration of all the fibers destined for each motor and sensory unit. The course of the regeneration indicated that there had been little, if any, disturbance of the intraneural fascicular pattern, though the persistence of residual sequelae may be evidence that this had occurred in some small measure. All these features are characteristic of the type of injury referred to by Seddon [5] as axonotmesis.

On the other hand, evidence of a neurapraxic state was reflected in the recovery of muscles which occurred either simultaneously or within sufficiently brief intervals to exclude recovery on the basis of axons advancing distally over different fiber-lengths, and in the rapidity of recovery in individual muscles which were innervated at such distances from the lesion that this recovery could not possibly

have been due to the growth of axons at anything approaching the estimated rates. However, the considerable delay (up to sixty-three days) in the onset of motor recovery in cases which otherwise conform to this type is an unusual feature, and if they are to be included in the neurapraxic group the definition of the latter should be extended to include delayed motor recovery.

It would thus appear that in cases 214, 232 and 234 there was a mixed lesion, in which the greater proportion of the total number of fibers to every muscle suffered a prolonged axoplasmic disturbance not leading to peripheral degeneration, while the remainder suffered a sufficiently severe injury to lead to wallerian degeneration.

A study of the rate and order of motor regeneration in conjunction with the level of the lesion in cases 27, 114, 202 and 244 indicated that the injury was not uniform throughout the nerve. The early recovery of certain muscles and the order of that recovery could be explained only on the basis of delayed concussion or neurapraxia, while the course of regeneration pursued by the others was in conformity with the intrafascicular interruption of fibers, which has been termed axonotmesis.

The time and order of recovery of the muscles in cases 69 and 99 suggested that wallerian degeneration had preceded regeneration but that the fibers and tissues at the site of injury were not uniformly involved, as a result of which some fibers preceded others in the regenerative process.

The manner in which recovery appeared, the rate and order in which it proceeded and the end result in cases 77, 106, 118, 161, 185, 203, 231, 255, 258, 264 and 317 were proof of a lesion of the type defined as axonotmesis. Though the lesions were not of equivalent severity in these cases (see later section), the evidence indicated that all the fibers and tissues at the site of injury were in each individual case damaged to approximately the same degree, the changes involving peripheral degeneration, with the subsequent spontaneous reinnervation of the distal segment.

A comparison of the observed and the deduced pathologic condition of the nerve and the onset of recovery in each muscle in cases 202, 203 and 244 suggests that the appearance of the nerve at the time of injury is a fairly reliable guide to the probable duration of the entire regenerative process, though it is not necessarily an accurate guide to the condition of individual fibers, since neurapraxia may occur with what appear to be severe injuries and axonotmesis in nerves which seem to be normal.

RATE OF REGENERATION

Method.—The methods at present available for estimating rates of regeneration in peripheral nerves in man following injury have recently been summarized by Seddon, Medawar and Smith.[3]

In the present investigation an additional method has been employed for calculating the rate of regeneration of motor axons. It is based on the time interval between the injury and the onset of recovery in two muscles and the shortest distance to each of them from the site of injury.

The equation for estimating the rate of regeneration is derived in the following manner (figure):

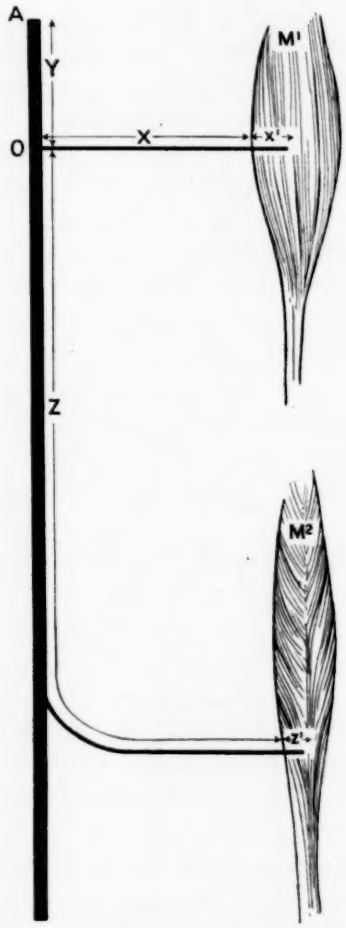

Diagram showing factors in derivation of equation for estimating rate of regeneration of the radial nerve.

A is a point on the nerve proximal to the site of origin of its branches

$y + x$ equals $L,^1$ the shortest distance to $M,^1$ the more proximally supplied of two muscles, from the point A

$y + z$ equals $L,^2$ the shortest distance to $M,^2$ the more distally supplied of two muscles, from the point A

x^1 *and* z^1 are the intramuscular distances in M^1 and $M,^2$ respectively, which must be covered by regenerating axons before voluntary contraction is possible

T^1 *and* T^2 represent the times elapsing, in days, between the injury and the appearance of contraction in M^1 and $M,^2$ respectively

d and D represent the initial delays elapsing before regeneration commences in axons destined for M^1 *and* $M,^2$ respectively

t^1 *and* t^2 are the times elapsing subsequent to the entry of axons into M^1 and $M,^2$ respectively, and before functional neuromuscular relations are reestablished and voluntary contraction is possible

The regenerating axons, therefore, travel $(y + x + x^1)$ mm. in $T^1 - (d + t^1)$ days and $(y + z + z^1)$ mm. in $T^2 - (D + t^2)$ days.

Assuming that

(*a*) The delay at A, the site of injury or suture, is the same for regenerating axons destined for M^1 *and* M^2

(*b*) The time taken by regenerating axons to travel the same distance in nerve fibers for different muscles is the same

(*c*) The distance which must be covered intramuscularly (x^1 and z^1) and the time (t^1 and t^2) elapsing in each instance before functional neuromuscular relations are reestablished and voluntary contraction is possible are identical.

it may be inferred that

The time taken to travel $(y + z) - (y + x)$ mm. is $T^2 - T^1$ days

Since $(y + z)$ and $(y + x)$ are the shortest routes to M^2 and M^1, respectively

The rate, R, in millimeters per day $= \frac{L^2 - L^1}{T^2 - T^1}$

Values for the lengths L^1 and L^2 were obtained for a series of muscles from an anatomic investigation of the radial, median, ulnar and sciatic nerves in 20 specimens. These will be reported separately. The lengths were measured directly along the nerve and its branches between a fixed point on the former and the site of entry of the branch into the muscle and in the case of multiple branches over the shortest route to the muscle. The exact position of the fixed point is, however, immaterial, since the distance along the nerve from it to the origin of the branch destined for the more proximally innervated muscle is common to the measurement for both the proximal and the distal muscles.

Values for the times, T^1 and T^2, calculated in days from the time of injury to the onset of recovery in the muscles were obtained from clinical studies of selected cases of peripheral nerve injuries in which the following conditions obtained:

1. Interruption of conduction was complete and associated with wallerian degeneration.

2. The onset and progress of recovery were such as to indicate uniform involvement of the fibers at the site of injury.

3. The onset and progress of recovery were such as to support the hypothesis that the axons commenced to regenerate at approximately the same time.

4. Any departure from the normal order of recovery could be satisfactorily explained on the basis of established anatomic variations.

In this way, factors which would invalidate the assumptions on which the equation depends were reduced to a minimum or were entirely eliminated.

It should be emphasized that this method is concerned only with the rate of growth of functionally mature fibers, since it depends on estimates of the progressive reestablishment of function. In common with all others, it neglects the distance

TABLE 3.—*Measurements of Rates of Regeneration of Radial Nerve*

A. Values for $L^2 - L^1$

Specimen	Distances, Millimeters *									
	BR.-E.C.R.L.	BR.-E.D.C.	BR.-E.C.U.	E.C.R.L.-E.D.C.	E.C.R.L.-E.C.U.	E.D.C.-A.P.L.	E.C.U.-A.P.L.	E.D.C.-E.P.L.	E.C.U.-E.P.L.	A.P.L.-E.P.L.
1	1	114	91	113	90	5	28	..	8	..
2	11	111	114	100	103	10	7	29	26	19
3	..	108	93	111	96	11	26	23	38	12
4	23	128	118	105	95	5	15	72	82	67
5	19	124	135	105	116	24	13	39	28	15
6	48	147	149	99	101	12	10	37	35	25
7	5	96	103	91	98	16	9	54	47	38
8	9	92	91	83	82	18	19	33	34	15
9	50	166	166	116	116	..	..	9	9	9
10	25	142	126	117	101	..	16	29	45	29
11	15	136	132	121	117	..	..	35	39	55
12	24	107	114	83	90	33	26	49	42	16
13	28	133	116	105	88	..	11	16	33	22
14	30	114	124	84	94	65†	55†	30	20	..
15	16	125	125	109	109	4	4	40	40	36
16	21	120	136	99	115	..	..	56	40	63
17	45	95	98	50	53	6	3	58	55	52
18	25	97	104	72	79	32	25	57	50	25
19	30	139	150	109	120	10	..	40	29	30
20	40	113	119	73	79	25	19	40	34	15
Mean of differences	25	120	120	98	97	15	15	39	37	30
Standard deviation	14	20	21	19	17	10	8	16	16	18

B. Values for $T^2 - T^1$

Nature of Injury	Times, Weeks									
	BR.-E.C.R.L.	BR.-E.D.C.	BR.-E.C.U.	E.C.R.L.-E.D.C.	E.C.R.L.-E.C.U.	E.D.C.-A.P.L.	E.C.U.-A.P.L.	E.D.C.-E.P.L.	E.C.U.-E.P.L.	A.P.L.-E.P.L.
Axonotmesis										
Case 77	2	7	7	5	5	2	2	4	4	2
Case 106	3	10	13	7	10	4	1	9	6	5
Case 161	1	8	10	7	9	4	2	7	5	3
Case 185	2	8	10	6	8	4	2	8	6	4
Case 203	..	7	7	7	7	4	4	4	4	..
Case 231	2	10	5	8	3	..	5	6	11	6
Case 255	..	10	10	10	10	2	2	8	8	6
Case 258	4	14	13	10	9	3	4	5	6	2
Case 264	..	..	..	9	9	2	2	11	11	9
Case 317	2	8	6	6	4	1	3	5	7	4
Mean of differences	2.3	9.1	9.0	7.5	7.4	2.9	2.7	6.7	6.8	4.6
Suture										
Case 40	..	..	..	14	15	6	5	6	5	..
Case 180	..	..	..	11	11	3	3	11	11	8
Case 282	5	15	14	10	9	3	4	8	9	5
Mean of differences	..	..	..	11.7	11.7	4.0	4.0	8.3	8.3	6.5

TABLE 3.—*Measurements of Rates of Regeneration of Radial Nerve—Continued*

C. Rates of Regeneration, in Millimeters per Day

Nerve Segment Over Which Rate Was Estimated	Axonotmesis: Distance, L, in Mm.	Time, T, in Weeks	Mean Rate from Mean L and T	Rate from L+ and T+	Rate from L— and T—	Suture (3 Cases Only)
BR. to E.C.R.L.	25 ± 14	2.3 ± 0.9	1.6	1.7	1.1	...
BR. to E.D.C.	120 ± 20	9.1 ± 2.2	1.9	1.8	2.1	...
BR. to E.C.U.	120 ± 21	9.0 ± 2.9	1.9	1.7	2.3	...
E.C.R.L. to E.D.C.	98 ± 19	7.5 ± 1.7	1.9	1.8	1.9	1.2
E.C.R.L. to E.C.U.	97 ± 17	7.4 ± 2.5	1.9	1.6	2.3	1.2
E.D.C. to A.P.L.	15 ± 10	2.9 ± 1.2	0.7	0.9	0.4	0.5
E.C.U. to A.P.L.	15 ± 8	2.7 ± 1.2	0.8	0.8	0.7	0.5
E.D.C. to E.P.L.	39 ± 16	6.7 ± 2.3	0.8	0.9	0.7	0.7
E.C.U. to E.P.L.	37 ± 16	6.8 ± 2.5	0.8	0.8	0.7	0.6
A.P.L. to E.P.L.	30 ± 18	4.6 ± 2.2	0.9	1.0	0.7	0.7

* In this table, BR. indicates brachioradialis; E.C.R.L., extensor carpi radialis longus; E.D.C., extensor digitorum communis; E.C.U., extensor carpi ulnaris; A.P.L., abductor pollicis longus, and E.P.L., extensor pollicis longus.

† Value discarded.

which must be covered intramuscularly by the regenerating axons before voluntary contraction is possible and the time elapsing between the entry of axons into the muscle and the appearance of voluntary contraction. However, these factors are constantly present in all muscles, and, though they are not necessarily equivalent, it is reasonable to assume that if any dissimilarity does exist it is so small as to be unimportant.

Since it cannot be assumed that the rate is constant over the entire length of the nerve, this method should not be employed for calculating rates between the first and the last muscle innervated by the nerve when a considerable distance separates them. The rates should be independently calculated for proximal and distal segments of the nerve, and muscles should be so selected that the distances between them are such that any diminution in rate which would occur over them, and which would thereby invalidate the equation, is reduced to insignificant proportions or is entirely eliminated. In this investigation, the rate was calculated separately over the proximal (brachioradialis to extensor carpi radialis longus; brachioradialis and extensor carpi radialis longus to extensor digitorum communis and extensor carpi ulnaris, respectively), intermediate (extensor digitorum communis and extensor carpi ulnaris to abductor pollicis longus) and distal (extensor digitorum communis, extensor carpi ulnaris and abductor pollicis longus to extensor pollicis longus) portions of the radial nerve. No attempt was made to calculate the rate of regeneration over extensive lengths, as would be the case if, for example, the brachioradialis and the extensor pollicis longus were used as the test muscles.

Advantages of the method here described are that it renders unnecessary a knowledge of the level of the injury and the delay occurring at that site before the commencement of regeneration. Furthermore, the rate of regeneration can be estimated separately over different segments of the nerve by selecting muscles which are innervated at different levels, a condition which, in turn, means that it is then possible to ascertain whether regeneration proceeds uniformly during the entire process or whether its rate diminishes progressively. It is not possible, however, to estimate by this means the rate over that section of the nerve which is proximal to the origin of its first branch, since the portion of the nerve pattern over which the rate is estimated actually commences at a point on the

main trunk which is distal to the origin of the branch to M^1 by the length of that branch.

The rate of regeneration can be estimated in any individual case, or an average rate, calculated from mean readings for T^1 and T,[2] can be obtained from observations in a large series of cases. With the former method the considerable and unpredictable range of variations in the length of the shortest fibers to the same muscle in different persons must be taken into consideration. This factor was not mentioned, and was apparently disregarded, by Seddon, Medawar and Smith[3] when calcuating, by another method, their rates of regeneration. When the rate is calculated on mean readings for L and T in a large number of cases, as has been done in this study, it is believed that this unpredictable element is reduced to a minimum. By averaging the lengths and times (L and T) for any group of muscles, those factors peculiar to an individual case which may influence the rate of regeneration are disregarded. However, it is an average estimate of the rate of regeneration which is being sought, since, regardless of the method employed, the rate peculiar to any individual case can be calculated only in retrospect—that is, after regeneration has advanced over suitable lengths of the nerve.

Values for $L^2 - L^1$ for the radial nerve are given in table 3 A. All measurements were made along the nerve and its branches from a point 10 cm. above the lateral epicondyle.

Values for $T^2 - T^1$ are given in table 3 B. Only cases 77, 106, 161, 185, 203, 231, 255, 258, 264 and 317 fulfilled the required conditions, while cases 40, 140 and 180 proved suitable for a study of rates of regeneration following nerve suture. In the few instances in this series in which two to three weeks separated examinations muscles showing recovery at the second examination were considered to have recovered midway between the two.

The mean rates of regeneration, calculated in millimeters per day between brachioradialis and extensor carpi radialis longus, brachioradialis and extensor digitorum communis, brachioradialis and extensor carpi ulnaris, extensor carpi radialis longus and extensor digitorum communis, extensor carpi radialis longus and extensor carpi ulnaris, extensor digitorum communis and abductor pollicis longus, extensor carpi ulnaris and abductor pollicis longus, extensor digitorum communis and extensor pollicis longus, extensor carpi ulnaris and extensor pollicis longus, and abductor pollicis longus and extensor pollicis longus are given in table 3 C.

No attempt has been made to estimate, by the method here described, the standard deviations of the rates of regeneration over those portions of the nerve pattern investigated. However, in studying the possible influence of the standard deviations of the lengths and of the times, which have been recorded, on the rates of regeneration, it seems reasonable to assume that in the regenerative process high and low values for the times would most probably correspond to high and low values, respectively, for the lengths. Calculations have been made on this basis, and the estimated rates for the high and low values of the lengths and times, respectively, have been included with the mean rates in table 3 C.

Results.—Except for a pronounced discrepancy in the rates calculated over the portions of the nerve pattern from extensor digitorum communis and extensor carpi ulnaris to abductor pollicis longus, there was little variation in the three rates calculated for each and corresponding portions of the nerve. A possible explanation of this discrepancy is the unusually high value obtaining for the lengths extensor digitorum communis and extensor carpi ulnaris, respectively, to abductor

pollicis longus in 1 specimen (case 14), since when this specimen was discarded for the purposes of estimating the rate of regeneration over these two portions of the nerve (as was done in calculating the rates recorded in table 3 C) the three calculated rates then approximated.

Comment.—From these results it is suggested that the mean rate over the proximal portions of the pattern is greater than that over the distal portions and that the difference in the mean rates is sufficiently great to indicate that there is a progressive diminution in rate as regeneration advances. It would appear, however, that in the initial stages the rate diminishes rapidly over the proximal portions of the nerve and then, fifty to one hundred days after the first appearance of recovery, becomes relatively constant at 0.8 mm. per day over the distal portions.

Though it is not justifiable to draw dogmatic conclusions on the basis of 3 cases, the evidence would suggest that the rate of regeneration following suture is, in the initial stages at least, less than that following axonotmesis but that later, one hundred to one hundred and fifty days after the first appearance of recovery, the rate approximates that following axonotmesis.

Seddon, Medawar and Smith [3] inferred from their calculations that "the rate of regeneration is initially as high as 3 mm. a day, and that it falls off progressively down to and then below a value of the order of 1 mm. a day about 100 days after recovery has started." However, they concluded that the rate could be regarded as "constant over the moderate ranges of time and distance over which the process was recorded in the great majority of the cases described." With their method for estimating rates of regeneration, they recorded rates of 1.6 ± 0.2 mm. per day following suture and of 1.5 ± 0.1 mm. per day in cases of axonotmesis. These values are in certain respects at variance with the results in this investigation. On the basis of data obtained from Stopford's records, these authors calculated that the rate of regeneration following suture was $0.56 \pm .03$ mm. per day, which approximates the rate calculated over the distal portions of the sutured nerves in the present study.

There was no significant relationship between the age of the patient (in this series the ages varied from 19 to 30 years) and the course of regeneration, and therefore it was not possible to determine whether or not regeneration proceeds at a faster rate in young persons.

LATENT PERIOD INTERVENING BETWEEN TIME OF INJURY AND ONSET OF RECOVERY

The following information has been correlated in table 4: (*a*) the agent responsible for the injury; (*b*) the level of the injury with reference to the lateral epicondyle; (*c*) the degree of infection and scarring;

(*d*) the time taken for the first and the last muscle to recover, together with the interval between these periods, and (*e*) the calculated initial delay, in weeks, occurring at the site of injury.

It is believed that in cases 77, 161 and 317 the nerve was damaged where it passed through the lateral intermuscular septum—anatomic studies have placed this point approximately 10 cm. above the lateral epicondyle. The nerve was sutured in case 282 at the distal end of the spiral groove and in cases 180 and 40 immediately above and below the supply to the brachioradialis, respectively.

The latent period preceding the onset of recovery comprises and is determined by (*a*) the initial delay, *t*, occurring at the site of injury and (*b*) the time, t^1, taken by the regenerating axons to advance from that point to the first muscle recovering. The level of the injury will influence the second component but not necessarily the first. Allowing for

TABLE 4.—*Shortest Distances (in Millimeters) to Muscles Supplied by the Radial Nerve* *

	Measurements Taken from Point 10 Cm. Above Lateral Epicondyle †		Measurements Taken from Lateral Epicondyle †			
	BR.	E.C.R.L.	E.C.U.	E.D.C.	A.P.L.	E.P.L.
Mean	82	105	102	102	114	139
Standard deviation	15	11	20	21	21	23

* These measurements were employed in calculating the initial delay.
† In this table, BR. indicates brachioradialis; E.C.R.L., extensor carpi radialis longus; E.D.C., extensor digitorum communis; E.C.U., extensor carpi ulnaris; A.P.L., abductor pollicis longus, and E.P.L., extensor pollicis longus.

the differences in the level of the lesion, initial delays of short and long duration produce an early and a late onset of recovery, respectively.

Component t^1 can be calculated from the distance from the site of injury to the first muscle contracting and the estimated rate of regeneration. The shortest distances to the muscles supplied by the radial nerve were measured in 20 specimens directly along the nerve and its branches between a fixed point on the former and the site of entry of the branch into the muscle. Measurements relevant to this paper are given in table 4, and from these the distance from the site of the injury to the first muscle contracting can be calculated provided the level of the injury is known with reference to the fixed point. Over the proximal sections of the nerve, between the brachioradialis and extensor carpi radialis longus, above, and the extensor digitorum communis, below, the rate has been found to be 1.9 mm. per day. Since, however, the rate has been shown to diminish progressively as regeneration proceeds, it is conceivable, and extremely likely, that the growth may be more rapid at higher levels than at those for which the rate of 1.9 mm.

was obtained. Since the rate for the section of the nerve between the level of the injury and the brachioradialis could not be calculated, that of 1.9 mm. per day has been employed in calculating t^1 in all cases. The initial delay may be calculated from the latent period and t^1. This was done in 15 cases, and the values are given in table 5. In the absence of additional cases of suture from which to obtain a more

TABLE 5.—*Values for Initial Delay in Regeneration in Fifteen Cases of Injury to Radial Nerve*

Nature of Injury	Level of Injury, Cm.	Infection *	Scarring *	Initial Delay, Weeks	First Contraction, Weeks	Last Contraction, Weeks	Difference
Axonotmesis							
Simple fracture							
Case 77	10.0	Nil	Nil	9.8	16	27	11
Case 161	10.0	Nil	Nil	6.8	13	28	15
Case 317	10.0	Nil	Nil	9.8	16	29	13
Gunshot wound							
Case 185	12.0	Nil	Nil	6.3	14	30	16
Case 203	9.0	Nil	Nil	14.6	20	31	11
Case 255	2.0	I	S	8.0—	8	26	18
Case 264	1.0	Nil	S	12.9	14	34	20
Gunshot wound + fracture							
Case 231	12.5	I	S	32.0	40	56	16
Case 118	9.0	I	S	10.6	16	28	12
Case 100	7.5	I	S	17.0	23	32-36	9-13
Case 106	5.0	I	S	14.6	17	36	19
Case 258	5.0	I	S	15.6	18	37	19
Suture							
Laceration							
Case 282	12.5	Nil	Nil	14.0	22	45	23
Case 180	4.0	Nil	S	16.6	20	42	22
Gunshot wound							
Case 40	5.0	I	S	15.9	20	40	20

* I and S indicate significant infection and scarring, respectively.

precise average rate of regeneration, that of 1.9 mm. was employed in calculating the initial delay in the 3 cases of suture studied in the present investigation.

Initial Delay Following Axonotmesis.—The level of the lesion has apparently no effect on the duration of the initial delay.

In general, the variation in the calculated initial delays may be accepted as an expression of the relative severity of the injury in each case. The delay was, as a rule, of longer duration in cases in which the lesions were due to gunshot injuries, particularly when these were associated with compound fractures of the humerus and considerable infection and scarring. Cases 118, 185 and 255, however, are exceptions.

Initial Delay Following Suture.—This varied from 14 to 16.6 weeks. The shorter interval (14 weeks) in case 282 could be attributed to the fact that the wound was clean and the nerve was not completely severed and was sutured at the time of the injury. In case 180 the nerve was sutured thirty-eight days after the injury, and,

though the wound was not infected, the residual scarring was considerable. In case 40 there was a considerable degree of infection of the wound in the initial stages and scarring, while secondary suture was not performed until eleven months after the injury. However, considering the complications operating in cases 40 and 180, the difference in the periods of delay is remarkably small. A possible explanation of this is that a well executed suture, in the absence of infection, converts the lesions in all cases into injuries of equivalent severity. The data in case 40 also indicate that a delay of eleven months before suture did not materially influence either the initial delay or the course of regeneration.

Comment.—From the data available, it would appear that the duration of the initial delay is a measure of the severity of the nerve injury. In establishing this relationship, the observations in the simple fracture and suture groups were of particular significance.

In the simple fracture group infection and scarring were absent, and the roentgenographic and clinical data indicated that the nerve had been damaged at a corresponding level in all 3 cases. From the nature of the causative injury and the order and rate of regeneration, which corresponded closely in all 3 cases, it appeared that the extent of the injury was similar and of minimal degree in each case. The initial delay was approximately 10, 10 and 7 weeks, respectively.

The course of regeneration in case 118, of the gunshot wound group, in which there were significant infection and scarring, closely resembled that observed in the simple fracture group. It seems reasonable to assume, therefore, that the extent of the injury in this case was similar and that infection and local scarring had provided no obstacle to regeneration.

Though the causative injury, the condition of the wound and the interval between the injury and the time of suture varied widely in the cases comprising the suture group, the course of regeneration corresponded fairly closely in the 3 cases. Here, disregarding the influence of infection and local scarring, the injury was known to be maximal in extent and the initial delays observed were 14, 15.9 and 16.6 weeks, respectively. The calculated initial delays in cases 100, 106, 203 and 258 approximated those in the suture group. Presumably, in these cases the injury was of greater severity than that observed in the simple fracture group.

Between these two groups will be found all intervening grades of severity of injury, which will account for intermediate variations in the initial delays. Thus, in cases of axonotmesis the severer the injury the closer will the course of regeneration approximate the sequence of events following suture.

The observed initial delay in case 231 was 32 weeks. This was the extreme maximum delay observed and was not approached in any other case. Its presence, however, is sufficient to indicate that delays beyond 17 weeks do occur.

Seddon, Medawar and Smith [3] claimed that " there is no doubt whatever that the latent period after suture is longer than that after axonotmesis." An examination of the initial delays recorded in table 4 provides evidence that this is not invariably the case.

INFLUENCE OF DURATION OF LATENT PERIOD ON SUBSEQUENT COURSE OF REGENERATION

The course of regeneration subsequent to the onset of recovery may be expressed in terms of the time taken to reinnervate the entire pattern, as measured from the onset of recovery in the first and the last muscle to recover. This period varied from 11 to 23 weeks. It was minimal in the simple fracture group and maximal in the suture group.

There are four possible explanations of the observed differences in the time taken to reinnervate the pattern.

1. The linear extent of the pattern is known to vary over wide limits in different persons. The recorded differences are of such magnitude that these alone could account for the observed differences in time.

2. The rate of regeneration may vary in different persons. It is extremely unlikely that the rate is a constant one, though the possible range of variations is unknown. It is improbable, however, that this factor alone would account for the observed differences in the time taken to reinnervate the pattern.

3. Some nerve fibers may be more severely damaged than others, and this may introduce a variation in the initial delay for different fibers. That this may occur has been deduced from the sequence of events following the injury in cases 27, 69, 99, 114, 202 and 244, in which the order of recovery was so deranged that the cases were discarded for the purposes of this investigation. To explain the variations in the time taken to reinnervate the entire pattern on this basis, the onset of regeneration in the fibers destined for either the first or the last muscle to recover, or both, must be delayed, though not in such a way as to disturb the normal serial order of recovery.

4. It may be that the over-all rate of regeneration is slower in cases in which the initial delay is longer, that is, in cases in which the injury has been more severe but in which it has, nevertheless, been equally distributed over all the fibers at the level of the injury.

If the duration of the initial delay is any guide to the severity of the injury, and there is some evidence to indicate that it is, then it

might justifiably be expected that initial delays of long duration would be associated with the longer periods taken to reinnervate the pattern. Reference to table 4 will show that in general this is so, particularly in the suture group, in which the injury is maximal in degree.

There are cases, however, which demonstrate that an early or late onset of recovery is not invariably followed by an accelerated or a retarded innervation of the pattern, respectively, such as might be expected had all the fibers been uniformly involved. If the severity of the injury were alone in question, then this evidence would indicate an injury of varying severity in individual fibers or fasciculi. The onset of regeneration must, then, have been unduly delayed in the fibers destined for either the first or the last muscle to recover or both, though without in any way disturbing the order of reinnervation (see paragraph 3).

The presence of so many variables makes it extremely difficult to assess the relative participation and contribution of each. Briefly, one or a combination of the following three factors may influence the time of reinnervation. Of these, the first was probably the most significant in the cases selected for this analysis.

(*a*) Variations in the linear extent of the pattern.

(*b*) Variations in the severity of the injury with reference to the entire cross sectional area of the nerve or to individual fibers or fasciculi composing it.

(*c*) Variations in individual rates of regeneration.

ESTIMATION OF PERIOD IN WHICH RECOVERY SHOULD APPEAR

The time when recovery, spontaneous or following suture, should make its appearance can be calculated from the following information:

1. With injuries (axonotmesis) which are minimal in degree and usually due to uncomplicated trauma, an initial delay up to approximately 10 weeks may be expected. If the lesion is more severe, as it is after suture or after severe gunshot wounds associated with fracture of the humerus, infection and extensive scarring, then a delay of about 4 months may be expected in all but the exceptional cases.

Seddon, Medawar and Smith [3] concluded, on the other hand, that an interval of 6 to 8 weeks is an "unduly long latent period." It would seem, however, that this delay is too short and would account for only certain minimal injuries.

2. When the level of the lesion is known, the time taken for the regenerating axons to cover the distance from the site of the injury to the brachioradialis or the extensor carpi radialis longus may be calculated at an average rate of 1.9 mm. per day.

In general, for a lesion situated 10 cm. above the epicondyle, the onset of recovery in the brachioradialis should not be delayed beyond approximately 4 months after "simple" injuries and 6 months after severe injuries or nerve suture. Admittedly, it is difficult to distinguish between simple and severe nerve lesions, since the nature and severity of the causative injury are by no means an invariable guide. However, as previously shown, lesions are as a rule more severe when due to gunshot injuries, when the wounds are infected, when there is considerable scarring or when the humerus is fractured.

Delays of 6 months do not adversely affect the subsequent course of regeneration or apparently that following suture when this is indicated. The maximum latent period observed before spontaneous regeneration became evident and proceeded to completion was 10 months, though such a delay must be unusual. In the majority of the cases spontaneous regeneration was well advanced at the end of 6 months and ultimately proceeded to complete restoration of function.

By adding from 11 to 23 weeks, according to the type and severity of the nerve lesion, to the date of onset of recovery in the first muscle to recover, it is possible to calculate the approximate time when voluntary contraction may be expected in the last muscle to be reinnervated. This time, of course, has no reference to the full restoration of function, which is not attained until several months, or even years, later.

It is not proposed to discuss the controversial issues regarding the time when nerves in which conduction is completely interrupted (though the morphologic state is unknown) should be explored, since this involves factors other than those within the scope of the present study. The following facts, however, have been established from this investigation:

1. The majority of such lesions regenerate spontaneously, with an end result which, even though it may not be complete recovery, is at least far superior to the result which could be expected from nerve suture.

2. In the majority of cases in which exploration of the nerve is demanded and undertaken irreparable damage to the nerve will be revealed.

3. Delay in the onset of regeneration for periods up to 10 months will not adversely affect the subsequent course of regeneration or apparently that following suture when this is indicated.

SUMMARY

Observations on the course and rate of regeneration of motor fibers following lesions of the radial nerve are described.

The end results in a series of 63 cases of such lesions, on which the observations are based, are briefly summarized.

Reference is made to the significance of variations in the serial order of motor recovery.

The pathologic character of the lesions is analyzed in terms of the course of regeneration.

A method for estimating rates of regeneration of functionally mature motor fibers in human peripheral nerves is described. With this method, rates of regeneration have been calculated over proximal and distal segments of the nerve below the origin of the branch to the brachioradialis. The results indicate that there is a progressive diminution in rate as regeneration advances.

In cases of axonotmesis mean rates of 1.9 and 0.8 mm. per day were obtained for the proximal and distal segments of the nerve, respectively. In cases of suture, mean rates of 1.2 and 0.6 mm. per day were obtained for the proximal and distal segments of the nerve, respectively.

Observations were made on the period intervening between the injury and the time when regenerating axons enter the distal segment —the initial delay—in cases of axonotmesis and suture.

(*a*) The duration of the initial delay is a measure of the degree of severity of the injury.

(*b*) The relationship of the duration of the initial delay to the reinnervation of the motor field subsequent to the onset of recovery is discussed in some detail. In general, initial delays of long duration are associated with longer periods for the reinnervation of the motor field. An early or a late onset of recovery is not, however, invariably followed by a subsequent accelerated or retarded rate of recovery.

(*c*) An initial delay of up to 10 weeks may be expected in cases of injuries which are minimal in degree and which are usually due to uncomplicated trauma. If the lesion is more severe, as it is after suture or after severe gunshot wounds associated with a fracture of the humerus, infection and intensive scarring, then a delay of approximately 4 months may be expected. It is, however, difficult to distinguish between simple and severe nerve lesions, since the nature and severity of the causative injury are by no means an invariable guide.

From a knowledge of the presumed initial delay, the level of the lesion and the rate of regeneration, it is possible to ascertain when recovery, spontaneous or following suture, should be expected.

By adding 11 to 23 weeks, according to the type and severity of the nerve lesion, to the date of onset of recovery in the first muscle to be reinnervated, it is possible to calculate the approximate time when

voluntary contraction may be expected in the last muscle to be reinnervated.

The maximal period intervening between the injury and the onset of recovery—latent period—before spontaneous regeneration became evident and proceeded to completion was 10 months. In the majority of nerves regenerating spontaneously, however, recovery had appeared at the end of 6 months.

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ELECTRIC SHOCK THERAPY OF ELDERLY PATIENTS

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THE TREATMENT of elderly patients by means of electric shock constitutes one of the serious problems of this form of therapy. The problem centers about the difficulty of deciding whether the mental illness is sufficiently severe to warrant treatment in the face of physical handicaps. Many patients over 65 show no gross physical defects; others manifest various degrees of cardiovascular-renal impairment which increase the hazards of treatment significantly. The present study considers a series of 53 patients each over 65 years of age who have been given electric shock therapy at the Albany Hospital during a period of three and one-half years. An attempt is made to evaluate the indications and contraindications for treatment, as well as the results and complications in this series.

TABLE 1.—*Distribution of Patients by Age and by Year of Treatment*

Age Group, Yr.	1941	1942	1943	1944	Total No.
65-69	5	4	14	12	35
70-74	..	1	6	5	12
75-79	..	1	..	3	4
80-82	..	..	..	2	2
	5	6	20	22	53

CASE MATERIAL

Incidence.—Table 1 presents the distribution of the patients by age and by year of treatment. It will be noted that in 1941 and 1942 only 5 and 6 patients, respectively, over 65 were treated. In 1943 the figure increased to 20; and during 1944, 22 patients were treated. Thirty-five of the patients were in the age group from 65 to 69; 12, in the group from 70 to 74; 4, in the group from 75 to 79, and 2 were 82 years of age.

Diagnosis.—The distribution of patients according to diagnosis is presented in table 2. The majority of the patients were listed as suffering from a depres-

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sion, 36 falling in this category. There were, in addition, 4 with manic states, 7 with psychoneuroses and 6 with paranoid psychoses. The condition of the depressed patients was chiefly designated as involutional melancholia, but 6 of them possessed a sufficient cyclothymic background to be considered as having a manic-depressive depression. The majority of the depressed patients had no previous history of mental illness, but 8 of them required a second or still additional series of treatments in the course of the three and one-half years covered by this survey. One patient has had four such series within three years, with a total of more than forty electroconvulsive treatments, showing fair to good recovery from her depression at each episode. There were reactive or situational factors in several cases.

There were 4 patients whose condition was diagnosed as manic-depressive psychosis, manic type, 1 of whom had two attacks and another four attacks during a three year period. The paranoid psychoses of the 6 patients resembled closely the typical paranoid state of the involutional period. The 7 patients classified as having a psychoneurosis each manifested a degree of concomitant depression. One displayed severe hypochondriasis with a strong background of anxiety. The 6 other patients were designated as having severe anxiety states with features of depression.

Physical Status.—Cardiovascular Status: A patient was considered to show little or no cardiovascular impairment when no clinical signs of heart disease

TABLE 2.—*Distribution of Patients by Diagnosis*

Diagnosis	Number
Depression	36
Manic psychosis	4
Psychoneurosis with depression	7
Paranoid psychosis	6

were apparent, the electrocardiogram was normal and the blood pressure was below 160 systolic and 100 diastolic. Twenty patients were found to fulfil these criteria. The remaining 33 patients showed various grades of cardiovascular defect, from uncomplicated hypertension to actual heart failure, including pulmonary edema and auricular fibrillation. The most common indication of cardiac decline was electrocardiographic evidence of myocardial damage of some degree.

The patient with the most severely injured heart was a 65 year old woman suffering from severe depression and hypochondriasis, whose condition was diagnosed in December 1941 as auricular fibrillation with mild failure of the right side of the heart. Her electrocardiogram revealed "sinus arrhythmia with shifting pacemaker, left axis deviation and frequent ectopic ventricular beats." She was given nine electroconvulsive treatments, without complication, and was discharged as somewhat improved, to return for ambulatory treatment. She returned to the hospital in February 1944, again severely depressed, but a heart attack five months previously had rendered her physical condition so precarious that further electrotherapy was deemed inadvisable at this time. Because of her extreme agitation and depression, she was returned to the hospital in March 1944 and given two electroconvulsive treatments, after which she became dyspneic and pulmonary edema developed. The electric shock treatment was discontinued, and the patient rallied under supportive treatment. She was discharged with her psychiatric condition unimproved.

Several patients showed clinical and roentgenographic evidence of a moderately enlarged heart, and at least 2 had a greatly enlarged heart. Electrocardiograms revealed pronounced left axis deviation in several instances. The electrocardiographic reports also included such descriptions as "diffuse myocardial damage," "left ventricular enlargement," "definite evidence of myocardial damage," "possible coronary disease" and "suspicious evidence of arteriosclerotic heart disease." One patient presented a history of coronary occlusion one year before, followed by full clinical recovery. Several patients with systolic blood pressures of over 200 mm. were treated, including a 75 year old woman with a pressure of 270 systolic and 176 diastolic.

None of these patients gave clinical evidence of progression of the cardiovascular impairment as a complicaton of therapy. On 2 patients electrocardiograms were taken both before and immediately after an electroconvulsive treatment. One of these patients showed no significant change, revealing the same moderate degree of myocardial damage after treatment as before. The second patient also presented some evidence of myocardial damage before electroconvulsive treatment but showed "improvement in the condition of the heart muscle" immediately afterward.

Although cardiovascular impairment was by far the most important finding in the physical examination, several patients displayed other physical defects. A 67 year old woman suffered from tic douloureux in 1940, and section of the trigeminal nerve was performed. She subsequently had staphylococcic meningitis, which cleared after intensive treatment, but she was left with residual paralysis of the left leg, weakness of the right leg and incontinence of urine. Roentgenograms of the lumbar portion of the spine revealed extensive destruction of the joints between the bodies of the first and second lumbar vertebrae and between the twelfth dorsal and the first lumbar vertebrae, with prominent kyphosis. She became severely depressed after her return home and, after a considerable period of unavailing treatment, was given several courses of electroconvulsive therapy, at first with erythroidine, a curare-like drug, and later without. She made a good, but not lasting, recovery each time, receiving about forty treatments altogether, without impairment of her physical condition.

Another patient, a man aged 72, had a dorsal kyphosis, which prevented any significant degree of extension of the thoracic portion of the spine. A third patient, a man of 67, showed small bilateral inguinal hernias. A woman of 70 had a 4 plus Wassermann reaction of the blood, with a negative reaction of the spinal fluid. Asthma, with signs of emphysema, was present in a man of 65. A man of 82 had a large ventral hernia. In none of these patients did untoward physical results appear.

Duration of Treatment.—The average stay in the hospital for this group of patients was twenty-three days, with a range of from six to forty-two days. The number of electric shock treatments administered averaged about six per admission. The usual procedure following admission was a physical study of the patient, special care being devoted to an evaluation of the cardiovascular status. Treatment was therefore delayed for from three to seven days while roentgenograms and electrocardiograms were obtained, and medical consultation was requested when indicated. When begun, electroconvulsive treatments were given on a schedule of three times a week. A generalized grand mal seizure was obtained in each treatment. However, it was found necessary, somewhat more frequently than for younger patients, to space treatments more widely (i. e., twice a week) because of the confusion accompanying therapy.

Several patients quickly showed intellectual deterioration, necessitating cessation of treatment at an early stage. These were the patients in whom it had proved difficult to determine the degree of dementia as compared with the degree of depression and who were given treatment as a last resort. One patient showed a rapid decline in memory and comprehension after only two electroconvulsive treatments. Another patient, aged 77, became more agitated and confused with each succeeding convulsive treatment and was given a rest of ten days after the first two treatments, but manifested even more severe agitation when treatments were resumed. Therapy was therefore discontinued after four shocks. A third woman, aged 70, had a similar clinical course and showed extreme agitation after six electroconvulsive treatments.

On the other hand, a small number of patients showed gratifying response with as few as two to six electroconvulsive treatments. The oldest patient in the group, a man of 82, recovered completely from a severe depression after only two treatments. He became depressed again two months later, returned to the hospital and was discharged after only two electroconvulsive treatments, without untoward results. The longest course of treatments for a single admission was twelve, resulting in definite improvement. Several patients, however, were readmitted several times, 2 patients each receiving more than thirty electroconvulsive treatments, over a period of about sixteen months. These included ambulatory electric shock treatments, in addition to treatment in the hospital.

TABLE 3.—*Outcome of Electric Shock Therapy*

	For 43 Patients Admitted Only Once	For 10 Patients with Multiple Admissions (Total 24)	For Entire Group (53 Patients, 67 Admissions)
Recovery	10	4	14
Much improvement	16	9	25
Improvement	9	10	19
No improvement	8	1	9
	43	24	67

Outcome.—Of the series of 53 patients, 43 were admitted only once, whereas 10 required two or more courses of treatment. The outcome of treatment for each group is indicated in table 3. In the group of patients with single admissions, it will be noted that 35 patients showed some degree of improvement, most of them falling in the category of those whose condition was "much improved." A patient was considered as "recovered" when both physician and family judged that he was as well after treatment as he had been before his illness and was able to resume his responsibilities in every sphere. A patient's condition was designated as "much improved" when he made an almost complete readjustment but still required an occasional psychiatric check-up. The condition was said to be "improved" when the patient was able to return home and make a partial social adjustment but was still incapable of assuming more than fractional responsibilities and still demanded considerable psychiatric care. The condition was designated as "unimproved" when the patient required commitment to a state hospital because of the palpable failure to mend. In most instances the diagnosis in the last group had been difficult because the degree of intellectual deterioration as compared with the magnitude of depression was impossible to estimate. The electric shock therapy, however, made the dementia more apparent, whereas at the same time the patient's behavior failed to improve.

The 10 patients who required multiple admissions showed a similar curve of improvement except that it was more heavily weighted in the range of those who were "much improved" and "recovered." None of this group was committed to a state hospital after the last admission in which electrotherapy was given, and most of them were discharged as at least "much improved." The number of admissions ranged from two, for the majority, to four, for several patients. The intervals between admissions extended from one to twelve or more months. In the entire group of 53 patients, with 67 admissions, 56 admissions, or 83.5 per cent, terminated with the patient's being pronounced "recovered," "much improved" or "improved."

When the outcome of treatment is viewed from the standpoint of diagnosis, it is evident that all groups show both successes and failures (table 4). The number of patients in each category outside the depressions is too small to permit the drawing of conclusions, but in each class of patients except those with paranoid psychoses the majority showed evidence of improvement. Of the 6 paranoid patients, 3 showed improvement and 3 were not improved. The

TABLE 4.—*Final Outcome According to Diagnosis*

	Depression	Psychoneurosis	Manic State	Paranoid Psychosis
Recovery	11	1	..	..
Much improvement	15	1	2	2
Improvement	4	5	..	1
No improvement	6	..	2	3
	36	7	4	6

8 patients who recovered all presented depressions of varying severity, and only 6 in the group of depressed patients required commitment.

Complications.—There were no serious complications of treatment in the entire series except for the patient aforementioned who manifested congestive heart failure with auricular fibrillation before treatment and who became worse as the electroconvulsive treatments proceeded. All the other patients were discharged in as sound a physical condition, so far as could be discerned, as they displayed on admission. One patient had a questionable fracture of one rib. No significant difference between this group of elderly patients and younger patients was disclosed with respect to recovery from the seizure. There were, however, several occasions when artificial respiration was necessary, and 1 patient showed sufficiently severe respiratory difficulties after the second convulsive treatment to warrant discontinuing the treatments. There was no increase in the number of complaints about soreness of the back, and in no case was this complication severe enough to require roentgenographic examination of the spine. One patient complained for several days of moderate soreness of one arm.

Several patients regularly evinced excitement after the seizure, but this was controlled, as in younger patients, by intravenous injection of sodium amytal, in a dose of 4½ grains (0.29 Gm.).

COMMENT

The voluminous literature on electric shock therapy carries many scattered references to the treatment of aged patients, but few detailed

reports are available. Cash and Hoekstra [1] (1943) reported on a group of 84 patients with affective disorders, of whom 4 were over 70 and 10 over 60 years of age. Of this group, 64 per cent recovered, and 35 per cent showed social remissions with residual symptoms. The patients were treated with curare, without traumatic complications. No special reference to the cardiovascular status of the patients was made except for the statement that "the best results are obtainable in the older age groups, and complications are of no greater incidence than in the younger patients." The author noted, also, that treatment should not be withheld when disease of the coronary arteries is present unless there is evidence of cardiac decompensation.

Evans [2] reported on the treatment of a series of patients 17 of whom were over 60 and 5 over 70 years of age. The proportions of this group given electric and metrazol shock therapy are not stated. The author mentioned the case of a 74 year old woman with electrocardiographic evidence of complete left bundle branch block who responded well to twenty electric shock treatments. Two women over 60, with systolic blood pressures over 200, were successfully treated. Kline and Fetterman [3] reported on electrocardiographic studies of a group of 42 patients of whom 5 were over 60 and 1 was over 70. Electrocardiograms were taken before and after induction of a major convulsion. There were 5 patients in the series with abnormal cardiovascular systems, of whom 3 had hypertension, but none showed electrocardiographic abnormalities before or after treatment. A fourth patient was a 55 year old woman whose "angina pectoris" had been treated by the surgical establishment of a collateral coronary bed. She, too, showed no electrocardiographic alteration. The fifth case was that of a man aged 58 with rheumatic valvular disease and cardiac enlargement.

Kalinowsky [4] discussed electric shock therapy, mentioning 1,500 cases but did not mention age as a contraindication. Evans [5] studied 50 patients over the age of 50 who had had one or more convulsions induced either by metrazol or by electric shock; of this group 17 were over 60 and 5 over 70. It has been our experience that patients between 50 and 65 years of age may be validly considered to fall in the same

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1. Cash, P. T., and Hoekstra, C. S.: Preliminary Curarization in Electric Convulsive Shock Therapy, Psychiatric Quart. **17**:20-34, 1943.

2. Evans, V. L.: Physical Risks in Convulsive Shock Therapy, Arch. Neurol. & Psychiat. **48**:1017 (Dec.) 1942.

3. Kline, E. M., and Fetterman, J. L.: Electrocardiographic Changes Following Electrically Induced Convulsions, Am. Heart J. **24**:665-670, 1942.

4. Kalinowsky, L. B.: Electric Convulsive Therapy with Emphasis on Importance of Adequate Treatment, Arch. Neurol. & Psychiat. **50**:652-660 (Dec.) 1943.

5. Evans, V. L.: Convulsive Shock Therapy in Elderly Patients: Risks and Results, Am. J. Psychiat. **99**:531-533, 1943.

category as young and middle-aged patients so far as risks of treatment are concerned. In the 50 to 65 year group, the hazards of treatment are apparently not significantly raised, and the expected results approximate those found in the lower age groups. In patients over 65, however, the proportion of persons with cardiovascular impairments, manifest or latent, is so high that each patient becomes a problem in which the cardiovascular threat to life when the treatment is given must be weighed against the magnitude of the mental illness.

Diagnosis: Problem of Determination of Intellectual Impairment.—The cardinal problem in diagnosis is to ascertain whether there is present any true senile intellectual impairment and to determine the magnitude of this impairment. Patients suitable for treatment are those with definite psychotic elements of depression, mania or the paranoid state who do not show any appreciable degree of senile dementia. The differentiation between the retardation of depression and the dulness of dementia is sometimes difficult. The delay in the responses of the depressed patient may be misinterpreted and taken for inability to comprehend the questions asked. If care and patience in appraising the intellectual resources are exercised, however, it can be demonstrated that memory, orientation and reasoning are unimpaired. We have found useful a simple memory test developed in this hospital [6] whereby gross defects in remembering may be detected within a few minutes.

If the patient is stuporous, or so mute and underactive that the presence of intellectual defect cannot be determined, it is possible to allay this condition by means of an intravenous injection of sodium amytal. This drug, injected in amounts of from 1 to 8 grains (0.065 to 0.52 Gm.) serves in the majority of cases to break through the retardation and to elicit adequate responses to allow evaluation of memory and orientation. Information evoked in this way should be weighed in conjunction with the data supplied by the informants. It may be impossible to ascertain definitely whether or not a mild degree of senile dementia is present in addition to the more acute depression; the decision for or against treatment should be made with reference to the condition of the patient before the onset of the acute phase of the present illness. If there had been good adjustment, a chance taken to return to this status would seem desirable.

It was noted in the section devoted to the duration of treatment that several patients displayed definite intellectual deterioration after only two or three electroconvulsive treatments. The difficulty in evaluating the mental status is demonstrated in the following cases:

An agitated patient aged 75 had a disorder diagnosed as both paranoid and intellectual dementia. The weight of each factor could not be satisfactorily

6. Feldman, F., and Cameron, D. E.: The Measurement of Remembering, Am. J. Psychiat. **100**:788-791, 1944.

assayed before treatment. She had shown mental changes over a period of about ten years, in the form of seclusiveness, negativism and paranoid trends, and just before admission had become untidy, noisy, destructive, obscene, confused and disoriented. In the hospital the patient was so overactive and assaultive that no appraisal of her orientation and memory was feasible. She was given a series of electric shock treatments, in response to which she became much quieter and eventually fairly tractable. However, it became obvious that there were significant changes in the direction of dementia, shown in her persistent disorientation and confusion; and it was finally considered advisable to transfer her to a state hospital.

A second patient, a man of 70, entered the hospital with severe depression, marked by the delusion that the milk produced on his farm was poisonous. Evaluation of his mental status seemed to reveal, in addition to the melancholia and delusions, a significant degree of confusion, disorientation and impairment of memory. It was not possible to gage the amount of dementia, however, because of his retardation, and electroconvulsive therapy was instituted, the risks and prognosis having been explained to the family. After seven electroconvulsive treatments the depression lifted, the delusions disappeared and it was possible to determine that the patient's intellectual resources were very good indeed. He was discharged to return home as much improved.

Effectiveness of Treatment.—The value of treatment is seen in the high proportion of patients returned to their homes as either recovered or much improved. The figures for improvement compare favorably with those obtained in the treatment of younger patients with similar conditions, especially the depressions. The paranoid states responded least well, with 3 failures among 6 patients. The psychoneuroses did not show complete recovery, but in the majority of instances significant inprovement occurred. A woman aged 68 showed few elements of true melancholia but presented a twenty year history of severe hypochondriasis, having undergone eight major operations. During the few weeks before admission she had become increasingly tense and had begun to fear that she might become mentally ill. She was agitated but in good contact and constantly recounted her illnesses, with a painful fidelity to detail and usually with visible enjoyment. She improved significantly with electric shock treatment and was able to return to her household.

Hospital Care of Patients.—In general, elderly patients pose the same problems as younger patients with similar conditions except that they must be examined frequently and with especial care for signs of heart failure. The degree of agitation in this series of patients was variable, but in several the overactivity was so great that constant restraints and sedation were necessary to prevent self injury and exhaustion. Feeding became a major problem at times, and administration of nourishment by means of gavage or clysis was often inadequate before shock treatment was instituted. A number of patients constituted suicide risks, and the usual precautions were taken. The

patients were urged to be up and about and were kept busy about the ward when possible.

Complications of Therapy.—It has been noted that no complications resulted in the present series except for increased cardiac failure in 1 patient. The hazards of electric shock therapy in elderly patients, the literature on which was reviewed at the beginning of this section, can be seen to be concerned primarily with cardiac involvement. The cardinal problem from the standpoint of complications is that of the probability of death with mounting age. This question is discussed in the next section of this paper.

Among other complications, one would expect a greater frequency of fractures in elderly patients; but no reliable data on this score were discovered in the literature, and no fractures occurred in our series except for a questionable fracture of a rib. The possibility of increased danger in elderly patients during the period of respiratory depression immediately following the convulsion is suggested by the fact that 1 patient in this series experienced sufficiently severe respiratory difficulties after her second seizure to make further treatment inadvisable. Again, it should be stressed that the risks must be balanced against the possible benefits.

Association of Age with Fatalities from Electric Shock Therapy.—No deaths occurred among the elderly patients in our series. It was thought worth while, however, to survey the literature for deaths associated with electric shock therapy in order to determine the role of advanced age.

There is reference in the literature[7] to 19 deaths attributed to electric shock therapy, and to this number may be added a fatality occurring in this hospital. Many of the reported cases are not well documented, and in at least 3 cases death took place more than a month after the last treatment. If these cases are excluded from

7. Hamsa, W. R., and Bennett, A. E.: Traumatic Complications of Convulsive Shock Therapy, J. A. M. A. **112**:2244-2246 (June 3) 1939. Hayman, M., and Brody, M. W.: Metrazol Therapy in Schizophrenia: Report of a Fatal Case with Autopsy, ibid. **112**:310-311 (Jan. 28) 1939. Heilbrunn, G., and Weil, A.: Pathologic Changes in the Central Nervous System in Experimental Electric Shock, Arch. Neurol. & Psychiat. **47**:918-930 (June) 1942. Hoffman, M. G.; Sandler, N., and Hecht, H.: Paroxysmal Auricular Fibrillation Complicating Metrazol Shock Therapy, Am. J. Psychiat. **97**:372-379, 1940. Impastato, D. J., and Almansi, R.: A Study of Over Two Thousand Cases of Electrofit-Treated Patients, New York State J. Med. **43**:2057-2064, 1943. Androp, S.: Electric Shock Therapy in the Psychoses, Psychiatric Quart. **15**:730-749, 1941. Bellet, S.; Kershbaum, A., and Furst, W.: The Electrocardiogram During Electric Shock Treatment of Mental Disorders, Am. J. M. Sc. **201**:167-177, 1941. Cleckley, H., and Egleston, Du B., Jr.: Some Observations on Cardiovascular Changes in Shock Therapy, Psychiatric Quart. **15**:662-679, 1941.

consideration, the remaining 17 cases may be somewhat arbitrarily divided into three categories, as outlined in table 5. It must be stressed that this classification is a rough one, designed only to throw light on the degree of cardiac origin of electric shock fatalities. With this reservation in mind, it may be said that the first category includes those cases, numbering 9, in which the death was definitely or probably imputed to cardiac involvement. The second category consists of 7 cases in which either clinical or postmortem evidence was insufficient to reveal the probable cause of death but in which, so far as can be appraised from the reports, it may conceivably have been cardiac. The third category includes a single case of death ascribed to pneumonia.

In only 3 of the 17 cases enumerated was the patient over 65 years of age, and all have been placed in the first of the three aforementioned categories—i. e., cases in which the death was probably of cardiac origin. The distribution of ages for the 17 cases is indicated in column 2 of table 5; the 3 patients over 65 were 70, 70 and 75. It

TABLE 5.—*Cause of Fatalities Associated with Electric Shock Therapy: Seventeen Cases*

	Number	Age
Death definitely or probably due to cardiac failure	9	? 23 42 57 61 70 70 75
Cause of death questionable; conceivably due to cardiac failure	7	? 29 35 45 47 50 58
Other causes	1	59

will be seen that the ages in the remaining 6 cases in the first category, in which death was probably of cardiac origin, range from 23 to 61. None of the 6 patients was considered a bad risk on the basis of pretreatment clinical studies, whereas the 3 patients over 65 were thought to present greatly increased risks.

The number of deaths is too small for the derivation of sweeping conclusions, but it may be seen that the number of deaths of patients over 65, 3 among 17, should not be an overwhelming deterrent. This number may be contrasted with the figure of approximately 5 per cent for the group over 65 years of age in a large series of patients of all types who received electric shock therapy. (In the Albany Hospital, over the past three and one-half years, more than 1,000 patients have received electric shock therapy, among whom are included only 53 patients over 65.) It is probable that the figure of 5 per cent may be somewhat too large to apply to the population of the country as a whole. Contributing to lower this figure is the fact that many of the large series reported have included, exclusively or predominantly, schizophrenic patients, who fall principally into the lower age groups.

Ebaugh, Barnacle and Neubuerger [8] collected data on 7 cases of death associated with electric shock therapy and added 2 of their own. The ages of 6 of the 9 patients were between 45 and 58 years. One patient was 29, and the remaining 2 were 75 and 79 respectively. Both the patients from their own series were 57 years of age, and the deaths of both were attributable to cardiac impairment. One of these patients presented no clinical or electrocardiographic evidence of cardiac impairment but died of coronary thrombosis one and one-half hours after the twelfth grand mal seizure. The second patient, also, showed no clinical evidence of heart disease, and death may have been due to a severe vagotonic reaction, with cessation of both cardiac and respiratory activity. Of the 7 patients 3 died one to four months after treatment and the other 4 within three days after a treatment. The 3 patients whose deaths occurred after more than a month were 45, 56 and 79 years of age. The patients aged 45 and 79 were noted to have died of "cardiac failure." The patient aged 56 died three months after treatment, of "acute infection of the respiratory tract and septicemia."

The 4 patients dying within three days after a treatment are of more immediate interest. On 3 of these patients, aged 29, 50 and 58 respectively, no autopsy was performed, and the designated causes of death, namely, "coronary thrombosis and influenza," "involvement of central nervous system, preceded by respiratory failure" and "failure to regain consciousness," are necessarily vague. The last of these 4 patients, a man aged 75, died immediately after the third treatment, with cardiac fibrillation. There had been a pretreatment clinical diagnosis of advanced generalized arteriosclerosis, and this was confirmed at autopsy.

Jetter [9] reported 3 cases of death caused by electric shock administered to patients with diseased hearts. Of these patients, 1 was 23, the second 61 and the third 70. In the 23 year old patient autopsy showed acute focal nonsuppurative myocarditis and acute glomerulonephritis, both probably of several days' duration. The relationship between the electric shock, the eighth in the second series, and death was not clear, inasmuch as heart failure appeared only several hours after the treatment, and death occurred twelve or sixteen hours afterward. The second patient, a man of 61, died ten minutes after the eighth treatment, in severe circulatory collapse. Physical examination had disclosed no outstanding abnormalities, the size of the heart being normal, the rate regular and the blood pressure 156 systolic and 90 diastolic. Apparently, no electrocardiogram was taken. Postmortem observations included

8. Ebaugh, F. G.; Barnacle, C. H., and Neubuerger, K. T.: Fatalities Following Electric Convulsive Therapy: Report of Two Cases with Autopsy, Arch. Neurol. & Psychiat. **49**:107-117 (Jan.) 1943.

9. Jetter, W. W.: Fatal Circulatory Failure Caused by Electric Shock Therapy, Arch. Neurol. & Psychiat. **51**:557-563 (June) 1944.

extensive obliterating coronary arteriosclerosis and recent myocardial infarct. The third patient, aged 70, presented a sufficiently severe depression to warrant treatment in face of the known diagnosis of hypertensive vascular disease, cerebral thrombosis and old coronary thrombosis with bundle branch block. The electrocardiogram showed disease of the coronary arteries and left frontal bundle branch block. Death occurred twelve minutes after the beginning of the sixth treatment. Another case of fatality due to cardiac failure following electric shock therapy was mentioned by Levy, the death being attributed by Jetter [9] to vagotonic action. The age of the patient was not stated.

Cash and Hoekstra [1] reported the death of a man of 47 two hours after his fifth electric shock treatment, with curare. Autopsy did not reveal the exact cause of death, although its cardiac origin was considered likely. There was conspicuous sclerosis of the anterior descending coronary artery. Ziegler mentioned a patient of "about 70" who died at an unstated interval after an electroconvulsive treatment and in whom autopsy showed a badly damaged myocardium. No other details were given. He mentioned, too, a man of 68 with a history of having had coronary thrombosis several years before who responded well to therapy. Gralnick [10] reported the deaths associated with electric shock of 2 patients, aged 35 and 45. One patient died one week after the fourteenth treatment, in status epilepticus; autopsy was not obtained. The second patient died two days after the second treatment, the cause being unascertainable at autopsy, although cerebrovascular syphilis was present.

The death occurring in our hospital was that of a 42 year old white woman who was admitted to the Albany Hospital in February 1942 with a history of severe anxiety and depression, together with delusions and hallucinations. Physical and neurologic examinations gave normal results except that the patient appeared poorly nourished. Laboratory data were within normal limits. A diagnosis of schizophrenia was made, and electroconvulsive therapy was started in February 1942. The first seizure was immediate but predominantly affected the right side at the onset, spreading, to involve the whole body, over a period of forty seconds. After the seizure the patient was apneic for thirty seconds and then resumed normal respirations. Two days later the second electroconvulsive treatment was given. The first stimulus produced only a petit mal attack but was repeated with increased voltage, resulting in a grand mal seizure which lasted twenty-five seconds, and followed the same pattern as that on the first day. After the convulsion a few breaths were taken spontaneously, and then respiration stopped. The pulse

10. Gralnick, A.: Fatalities Associated with Electric Shock Treatment of Psychoses, Arch. Neurol. & Psychiat. **51**:397-402 (April) 1944.

became slow, and, despite artificial respiration, intravenous injections of metrazol and intracardiac administration of epinephrine, the patient died. Permission for autopsy could not be obtained.

SUMMARY

The results of electric shock therapy in a group of 53 patients aged 65 or more are reported. The difficulties in diagnosis, the contraindications to treatment and the complications and effectiveness of therapy are discussed. Three cardinal problems have emerged from this study.

1. The differentiation of true intellectual decline and other types of psychoses of the senium, especially depression, must be made. Suggestions for making this distinction are offered.

2. The significance of an impaired cardiovascular system in the patient with serious mental illness must be evaluated in terms of what the future holds for the patient with and without treatment.

3. When a diagnosis other than senile dementia can be made in a patient over 65, especially that of depressive, manic or paranoid psychosis, electric shock therapy should be considered. The only contraindications should be extreme defects in the physical state, particularly in the cardiovascular system.

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PATTERN OF METABOLIC DEPRESSION INDUCED WITH PENTOTHAL SODIUM

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THE INTRAVENOUS administration of pentothal sodium, an ultra-short-acting barbiturate, is used extensively for the production of clinical anesthesia. The clinical manifestations of cortical depression are evident within thirty seconds after the initial injection. During the action of the drug the patient passes through several phases of depression, depending on the influence of the drug on the various cerebral areas. Brazier and Finesinger [1] have shown with the aid of the electroencephalograph a depressant effect of pentothal sodium on the several parts of the cortex. First the frontal area was depressed, then the parietal and, last, the occipital. It has been demonstrated in vitro that barbiturates exert an inhibitory effect on cellular respiration of the brain,[2] particularly in the parts of the brain with the highest oxygen intake, such as the more cephalic regions, which suffer the most pronounced metabolic retardation.[3]

The venous drainage of the cerebral hemispheres and of the basal ganglia is not the same in all persons. Though the blood from the lower part of the brain stem, including the midbrain and the medulla oblongata, as well as the cerebellum, is equally represented in the two internal jugular veins, the venous return from the upper portions of

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Mrs. Ilse Memelsdorff made the determinations of glucose and lactic acid.

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1. Brazier, M. A. B., and Finesinger, J. W.: Action of Barbiturates on the Cerebral Cortex, Arch. Neurol. & Psychiat. **53**:51-58 (Jan.) 1945.

2. Quastel, J. H.: Respiration in the Central Nervous System, Physiol. Rev. **19**:135-183, 1939.

3. Himwich, H. E.; Sykowski, P., and Fazekas, J. F.: A Comparative Study of Excised Cerebral Tissues of Adult and Infant Rats, Am. J. Physiol. **132**:293-296, 1941.

the brain is not similarly arranged.[4] In the majority of persons the blood from the greater part of the cerebral cortex appears chiefly either in the right or in the left internal jugular vein, after passing through the superior longitudinal sinus, while the blood from the sinus rectus, coming partially from the basal ganglia, goes to the opposite side. Because of this arrangement of the venous drainage, it is possible to obtain blood from one internal jugular vein which is more representative of the cerebral hemispheres than is the blood of the opposite internal jugular vein, which, in turn, may be regarded as carrying the greater portion of the venous drainage from the basal ganglia. In some persons, however, the contents of the superior longitudinal sinus are divided about equally between the right and the left lateral sinus. In addition, a small percentage of persons possess a torcular Herophili, in which the return from the cerebral hemispheres and that from the basal ganglia are mixed. In that case the two internal jugular veins are equally representative of the upper and the lower part of the brain.

An opportunity to determine whether the cerebral hemispheres are depressed before other parts of the brain is made possible by the course of the cerebral venous return. If, for example, the administration of a drug reduces the arteriovenous oxygen difference of the blood from the side carrying the cortical component more than that from the opposite side and the cerebral blood flow is not accelerated, the results would indicate that the cerebral hemispheres are the first part of the brain to be depressed by that drug. Such results would cast light on the pattern of action of the drug used.

METHOD

On 11 of 12 patients control observations were made by drawing successive samples of blood from both internal jugular veins and from the brachial artery, with the use of procaine anesthesia. On another day pentothal sodium, in 1 per cent solution, was administered intravenously to each of these subjects, who had not received previous medication. For the injection, a needle communicating with a two way stopcock was inserted into the antebrachial vein, thus permitting the injection of the pentothal solution in one of two ways: either by syringe or by the intravenous drip method. The initial injection was slow, irrespective of the source of pentothal sodium, and varied with each patient. The solution was allowed to run at such a rate as to obtain any required level of depression

4. (*a*) Gibbs, E. L., and Gibbs, F. A.: The Cross Section Areas of the Vessels That Form the Torcular and the Manner in Which Flow Is Distributed to the Right and Left Lateral Sinus, Anat. Rev. **59**:419-426, 1934. (*b*) Batson, O. V.: Anatomical Problems Concerned in the Study of Cerebral Blood Flow, Federation Proc. **3**:139-144, 1944. (*c*) York, G. E.; Homburger, E. G., and Himwich, H. E.: Similarity of the Cerebral Arteriovenous Oxygen Differences on the Right and Left Sides in Resting Man, Arch. Neurol. & Psychiat. **55**:578-582 (June) 1946.

and to retain it over a given period. If it was desired to lighten the anesthetic effect after the initial injection, the administration of pentothal sodium was slowed or stopped. For deeper stages of barbiturate depression the administration of the drug was continued and accelerated.

When the patient was in light surgical anesthesia, three needles with stylets were inserted and made secure with strips of adhesive tape; a 19 gage needle was placed in each internal jugular vein and a 20 gage needle in the femoral artery. As a result of this preparation samples of blood could be drawn simultaneously from the three vessels. This simultaneity is an essential step in a comparison of the arteriovenous oxygen differences for the right and the left side for any given time.

The samples of blood were collected in glass containers over mercury, as previously described,[5] and were analyzed immediately for oxygen and carbon dioxide by the method of Van Slyke and Neill.[6] Analyses checked to within 0.2 volume per cent, and variations of 1 volume per cent or less between the arteriovenous oxygen differences for the right and for the left side were within the experimental error. The amount of glucose was determined with the technic of Hagedorn and Jensen,[7] and the lactic acid content, according to the method of Barker and Summerson.[8] The samples for the determinations of glucose and lactate were measured from a 1 cc. Van Slyke pipet. This procedure standardized the measurement of all samples of blood, whether for gases, glucose or lactic acid. Differences of 4 mg. of glucose and 1.2 mg. of lactate per hundred cubic centimeters were considered significant.

RESULTS

Oxygen.—In 11 resting patients the arteriovenous oxygen differences for blood from the two sides varied from 0.02 to 1.12 volumes per cent, with an average of 0.51 volume per cent, which is a value in agreement with the results of previous studies.[4c] After the injection of pentothal sodium two degrees of clinical changes were observed in the majority of patients, resulting in a classification of light and deep anesthesia. In light anesthesia the patients reacted to stimuli, whether their responses retained some voluntary element or were entirely involuntary. When the application of even painful stimuli failed to elicit muscular reactions, anesthesia was regarded as deep. In 17 of 22 observations at the lighter levels of anesthesia the arteriovenous oxygen differences for blood from either the right or the left internal jugular vein were preponderantly decreased. On 7 occasions the arteriovenous difference was decreased more on the right than on the left

5. Himwich, H. E., and Castle, W. B.: Studies in the Metabolism of Muscle: I. The Respiratory Quotient of Resting Muscle, Am. J. Physiol. **83**:92-114, 1927.

6. Van Slyke, D. D., and Neill, J. M.: The Determination of Glucose in the Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523-573, 1924.

7. Hagedorn, H. C., and Jensen, B. N.: Zur Mikrobestimmung des Blutzuckers mittels Ferricyanid, Biochem. Ztschr. **135**:46-58, 1923.

8. Barker, S. B., and Summerson, W. H.: The Colorimetric Determinations of Lactic Acid in Biological Material, J. Biol. Chem. **138**:535-554, 1941.

TABLE 1.—*Oxygen Content, in Volumes per Cent, of Cerebral Blood in Patients with Different Anatomic Patterns of Venous Return from Cerebral Hemispheres*

Patient No.	Condition *	Arterial Oxygen Content	Oxygen Content of Internal Jugular Venous Blood		Arteriovenous Oxygen Difference					Comment
			Right	Left	Right Side	Left Side	Smaller on Left Than on Right	Smaller on Right Than on Left	Equal on Two Sides	
	A. Predominant Component in Right Internal Jugular Vein †									
1	Control	18.22	12.24	11.12	5.98	7.10	....	1.12	....	
	Light	17.86	16.22	11.95	1.64	5.91	....	4.27	....	
	Light	17.17	13.67	11.84	3.50	5.33	....	1.83	....	
	Light	15.99	13.53	11.64	2.46	4.35	....	1.89	....	
	Deep	15.89	14.45	14.73	1.44	1.16	....	....	0.30	
	Deep	15.46	13.15	12.85	2.31	2.61	....	....	0.28	
2	Control	20.47	13.72	13.41	6.75	7.06	....	....	0.31	
	Light	19.65	16.50	13.61	3.15	6.04	....	2.89	....	
	Light	19.23	16.48	12.95	2.75	6.28	....	3.53	....	
	Deep	18.50	14.38	15.51	4.12	2.99	1.13	....	....	Fall in B. P. of 32 mm.
	Deep	.....	14.06	13.96	....	....	....	....	0.10	
	Deep	8.88	2.90	3.39	5.98	5.45	....	....	0.49	
3	Control	19.52	12.26	11.43	7.26	8.09	....	....	0.83	
	Light	18.35	12.94	10.18	5.41	8.17	....	2.66	....	
4	Control	18.94	11.22	12.11 *	7.72	6.83	....	....	0.89	
	Light	16.90	12.40	11.05	4.50	5.85	....	1.35	....	
	B. Predominant Component in Left Internal Jugular vein ‡									
5	Control	19.65	12.52	13.18	7.13	6.47	....	....	0.66	
	Light	18.12	12.95	14.02	5.17	4.10	1.07	....	....	
	Light	17.47	11.58	15.16	5.89	2.31	3.58	....	....	
	Light	16.33	10.53	14.18	5.80	2.15	3.65	....	....	
	Deep	.....	12.60	12.94	....	....	....	....	0.34	
	Deep	7.27	6.26	6.56	1.01	0.71	....	....	0.30	
6	Control	17.33	10.23	10.21	7.10	7.12	....	....	0.02	
	Light	15.59	10.23	14.66	5.36	0.93	4.43	....	....	
	Light	15.29	11.53	15.00	3.76	0.29	3.47	....	....	
	Deep	15.72	9.83	10.52	5.89	5.20	....	....	0.69	Fall in B. P. of 25 mm.
	Deep	13.45	11.97	12.97	1.48	0.45	....	....	1.00	
	Deep	6.37	2.93	3.71	3.44	2.66	....	....	0.78	
7	Control	18.29	11.71	11.31	6.58	6.96	....	....	0.38	
	Light	18.83	11.00	15.43	7.83	3.40	4.43	....	....	
	Light	18.80	10.04	16.76	8.76	2.04	6.72	....	....	
8	Light	16.82	12.67	15.22	4.15	1.60	2.55	....	....	
	Light	14.98	9.46	11.21	5.52	3.77	1.75	....	....	
9	Control	15.65	9.36	9.90	6.29	5.75	....	....	0.54	
	Light	14.21	8.11	11.41	6.10	2.80	3.30	....	....	
	C. Equal Division Between Right and Left Internal Jugular Vein §									
10	Control	19.78	10.72	11.21	9.06	8.57	....	....	0.49	
	Light	17.90	10.43	10.50	7.47	7.40	....	....	0.07	
	Light	17.08	10.97	10.88	6.11	6.20	....	....	0.09	
	Light	16.86	9.06	9.81	7.80	7.05	....	....	0.75	
	Deep	15.28	9.44	9.39	5.84	5.89	....	....	0.05	Fall in B. P. of 50 mm.
11	Control	18.05	10.72	11.10	7.33	6.95	....	....	0.38	
	Light	17.73	10.99	11.65	6.74	6.08	....	....	0.66	
	Deep	13.01	10.71	10.35	2.30	2.66	....	....	0.36	
12	Control	19.24	12.36	12.31	6.88	6.93	....	....	0.05	
	Light	17.98	11.27	11.35	6.71	6.63	....	....	0.08	
	Deep	15.56	13.30	12.01	2.26	3.55	....	1.29	....	Oxygen administration
	Deep	18.51	16.85	16.10	1.66	2.41	....	....	0.75	

* "Deep" and "light" refer to levels of anesthesia.

† Patients 1 to 4, listed in A, exhibited the cortical component of blood chiefly in the right internal jugular vein, as evidenced by the smaller arteriovenous oxygen difference on the right side than on the left side in all observations made during light anesthesia. The values for patient 1 are typical of this group. The control arteriovenous oxygen difference on the right side is 5.98 volumes per cent, and the difference falls to 1.64, 3.50 and 2.46 volumes per cent during light anesthesia. The control on the left side is 7.10 volumes per cent, and the difference is comparatively better sustained, at 5.91, 5.33 and 4.35 volumes per cent. During deep anesthesia the differences do not vary significantly and are reduced to their lowest levels, 1.44 and 2.31 volumes per cent on the right side and 1.16 and 2.61 volumes per cent on the left side.

(Footnotes continued on next page)

(table 1 A); in 10 determinations it was lowered more on the left than on the right (table 1 B), and in only 5 were the arteriovenous oxygen differences equal on the two sides (table 1 C). In 12 of 14

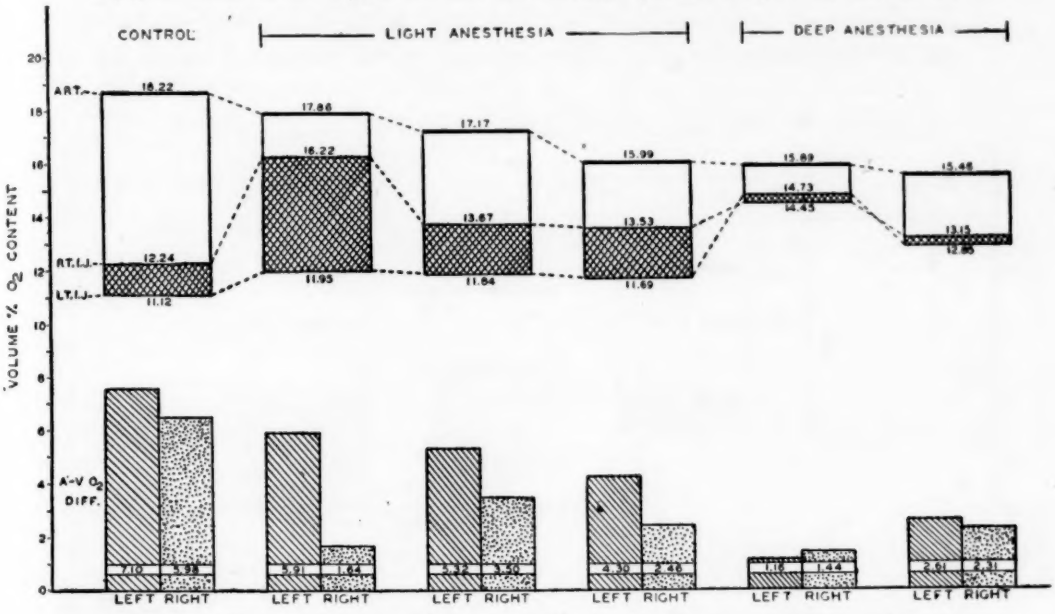

Fig. 1.—The results for patient 1 are illustrative of the group in which the major return of blood from the cerebral hemispheres appears in the right internal jugular vein. In all observations made on the subject during light depression, the arteriovenous differences on the right side were more reduced than those on the left side, while during deep anesthesia the differences on the two sides were at their lowest value and were in agreement with each other. The same data are presented in two ways: The columns in the lower part of the figure express the arteriovenous oxygen differences for the right and left sides in terms of volumes per cent, while in the upper portion are the actual values for the arterial and venous oxygen contents. The cross hatched area shows the difference in the oxygen content of the blood between the right and the left internal jugular veins. The gradual decrease of arterial oxygen is evident as the anesthesia becomes deeper.

FOOTNOTES TO TABLE 1

‡ In B are listed the results for patients 5 to 9, whose cerebral hemispheres are drained chiefly into the left internal jugular vein, as evidenced by the smaller arteriovenous oxygen differences on the left side than on the right when the subjects were under light anesthesia. Patient 5 typifies this group. The control arteriovenous oxygen difference on the left side is 6.47 volumes per cent and falls to 4.10, 2.31 and 2.15 volumes per cent during light anesthesia, while on the right side the control value is 7.13 volumes per cent and remains comparatively high, at 5.17, 5.89 and 5.80 volumes per cent. During deeper depression the arteriovenous oxygen differences are equal on the two sides and are within the experimental error. Note the progressive fall in the arterial oxygen content to the lowest value, 7.27 volumes per cent, during deep anesthesia and the reduction of the arteriovenous oxygen differences to 1.01 and 0.71 volumes per cent on the right and left sides, respectively.

§ In C, the results for patient 10 are typical of those obtained for patients 10 to 12, in whom the cortical blood is more equally divided between the right and the left internal jugular vein than it was in the patients listed in A and B. The arteriovenous oxygen differences on the right and on the left side are approximately equal. The control arteriovenous oxygen difference on the right side begins at 9.06 volumes per cent and falls to 7.47, 6.11 and 7.80 volumes per cent during light depression and to 5.84 volumes per cent during deep narcosis. The comparable values for the left side are 8.57, 7.40, 6.20 and 7.05, and 5.89 volumes per cent. In this subject the values obtained during deep anesthesia are not so reduced as were those in our other observations made during profound depression. Probably an accompanying greater fall in blood pressure slowed cerebral blood flow, so that more oxygen was removed from each cubic centimeter of blood passing through the brain.

results obtained with the deeper levels of anesthesia arteriovenous oxygen differences on the two sides were equally diminished. The alterations in blood gases showed that the results were correlated with the degree of anesthesia, so that with the lighter levels of anesthesia the arteriovenous oxygen differences (*a*) were decreased more sig-

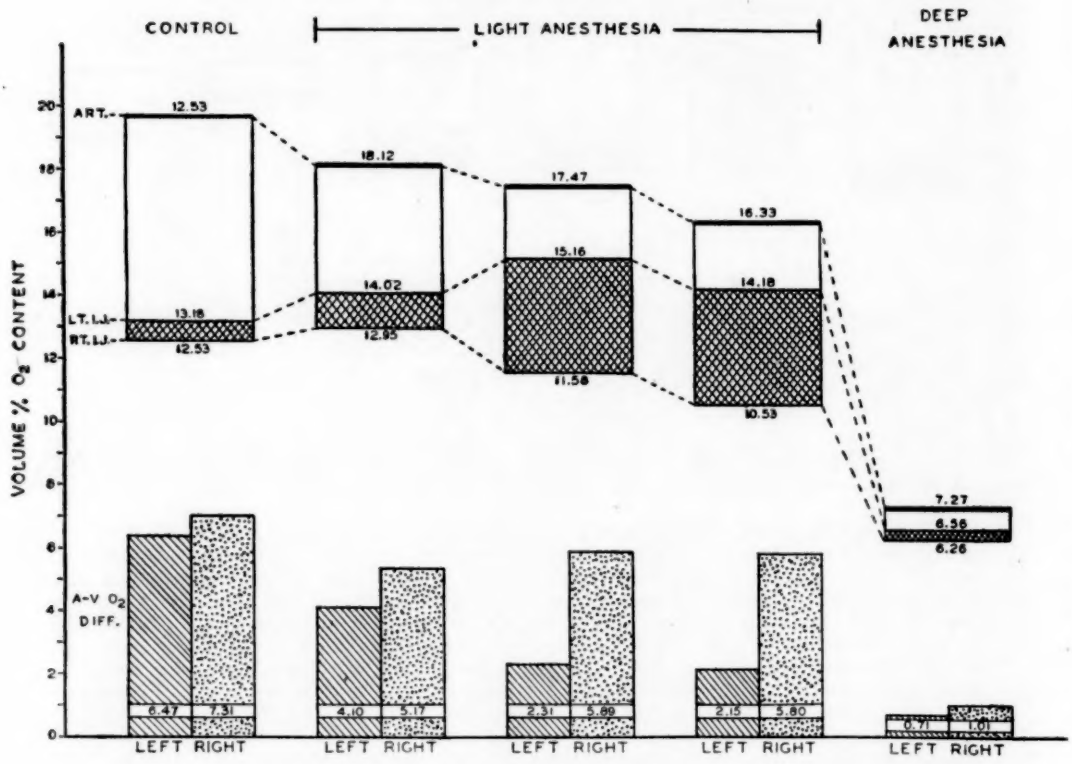

Fig. 2.—The data for patient 5 are characteristic of the group in which the cortical venous blood is carried chiefly by the left internal jugular vein. During light anesthesia, the arteriovenous oxygen difference on the left side is consistently smaller than that on the right side. During deep depression the arteriovenous oxygen differences are equal on the two sides and within the experimental error. The data are shown in two ways: The arteriovenous oxygen differences for the right and left sides are presented in the columns in the lower part of the figure, and in the upper portion are the values for the oxygen content. The cross hatched area shows the difference between the oxygen content of the right and that of left internal jugular vein. The profound depression of respiration in deep anesthesia is exhibited in the low oxygen content of the arterial blood.

nificantly on the right side than on the left in 4 subjects (table 1 A) and (*b*) were more reduced on the left side than on the right in 5 subjects (table 1 B). In 3 subjects only did the arteriovenous oxygen differences on the two sides vary only within the experimental error (table 1 C).

It must be emphasized that repeated observations yielded consistent patterns; i. e., if in the lighter stages of anesthesia the arteriovenous oxygen difference was smaller on the right side than on the left in the first observation it was smaller in all the succeeding onces. A typical result is that for patient 1 (fig. 1), whose right arteriovenous oxygen difference was smaller on the right side than on the left in each experiment made with administration of sufficient pentothal to secure light

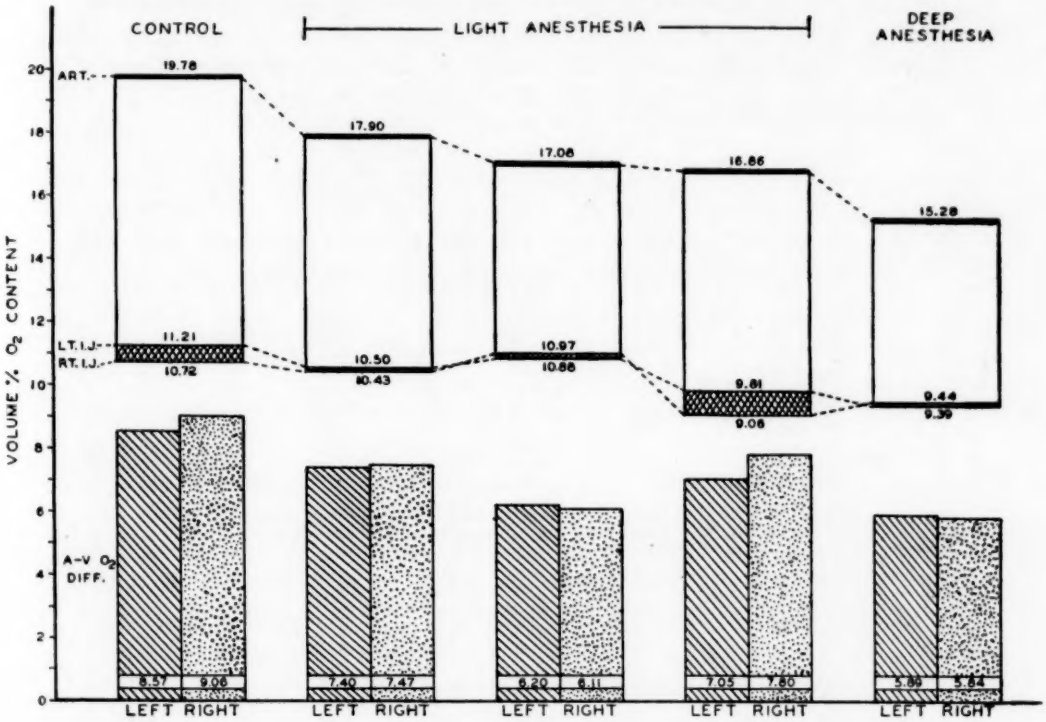

Fig. 3.—In patient 10 either a torcular Herophili was present or the branches of the superior longitudinal sinus divided its blood approximately equally between the two lateral sinuses. These data are presented twice, once in the lower columns, showing the paired values of the arteriovenous oxygen differences for the two sides, all of which vary within the error of the method, and, again, in the upper portion of the figure, with the values for oxygen content. The cross hatched portion shows the differences between the oxygen contents of the blood of the right and of the left internal jugular vein, none of which, however are significant. The comparatively large arteriovenous oxygen difference found during anesthesia is associated with a profound fall in blood pressure.

depression. Again, for patient 5 (fig. 2) the arteriovenous oxygen difference was smaller on the left side than on the right and remained so throughout light narcosis. In deep pentothal anesthesia, however, both patients exhibited arteriovenous oxygen differences which were equal and within the experimental error on the two sides, irrespective of the pattern displayed when the patient was lightly anesthetized. For patient 10 (fig. 3) the variations in the arteriovenous oxygen differ-

ences on the right and the left side were insignificant not only in deep anesthesia but also in light depression. This equality between the right and the left side is indicative either of the presence of a torcular or of a division in the blood of the superior longitudinal sinus between the two lateral sinuses.

Glucose and Lactate.—For the 3 patients for whom values are presented in table 1 C the oxygen contents of the right and of the left internal jugular vein were similar and within the experimental error.

TABLE 2.—*Gulcose and Lactic Acid Contents of Arterial Blood and of Blood of the Right and the Left Internal Jugular Vein*

Patient	Condition *	Arterial Blood, Mg. per 100 Cc.		Blood of Right Internal Jugular Vein, Mg. per 100 Cc.		Blood of Left Internal Jugular Vein, Mg. per 100 Cc.	
		Glucose	Lactic Acid	Glucose	Lactic Acid	Glucose	Lactic Acid
	A. Patients (Table 1C) in Whom Cerebral Venous Return Was About Equal on the Two Sides †						
10	Control	..	....	124	11.63	122	11.75
	Light	88	6.28	77	8.49	77	8.26
	Deep	84	....	81	....	81	....
11	Control	79	9.07	72	10.93	72	10.59
	Light	93	9.07	93	9.30	81	10.00
	Deep	101	12.10	97	8.35	97	8.35
12	Control	..	....	77	11.75	77	11.16
	Light	81	8.84	65	7.91	66	6.98
	Deep	77	9.19	74	5.82	74	5.47
	Deep + oxygen	77	5.47	77	9.07	77	6.40
	B. Patients (Table 1A and B) with Predominant Component of Cerebral Venous Return in Either Right or Left Internal Jugular Vein ‡						
2	Control	86	10.23	68	11.16	68	13.02
	Light	102	8.02	92	7.68	95	7.91
	Light	77	6.05	75	5.93	68	6.74
	Deep	101	10.93	93	7.79	99	6.98
6	Control	108	6.16	99	8.72	99	....
	Light	101	12.33	93	7.21	95	8.61
	Deep	97	8.49	90	8.49	95	7.79
	Deep	95	8.26	92	8.96	90	8.72
	Deep	92	6.40	90	6.12	90	6.51
	Deep	138	16.28	131	15.82	127	18.14
7	Control	95	7.44	88	11.16	88	13.49
	Light	99	12.44	88	9.88	92	9.19
	Light	95	11.63	88	11.05	92	7.09

* "Light" and "deep" indicate levels of anesthesia.

† The close agreement between the values for glucose and lactic acid contents of the blood in the right and the left internal jugular vein is apparent.

‡ The values for the glucose and lactate contents of the blood in the right and the left internal jugular vein are in less close agreement than are the comparable values in A.

The glucose and lactate contents of the two internal jugular veins of these 3 patients (table 2 A) displayed the same good agreement except for 1 observation each for glucose and lactate. For the other patients (table 1 A and B) a dissimilarity was noted between the oxygen content of blood of the right and that of the left internal jugular vein, especially during light anesthesia. The data on glucose and lactate for 3 patients of this group are presented in table 2 B. The agreement between the contents for the right and for the left internal jugular vein is not so close in most instances as it is in table 2 A.

When arteriovenous glucose differences for the two sides were considered together, irrespective of the source of the blood, it was found that in 11 resting patients the brain absorbed from 0 to 22 mg. from each hundred cubic centimeters of blood passing through that organ. The average arteriovenous glucose difference for 7 of the subjects on whom we had complete data was 9.1 mg. per hundred cubic centimeters in the resting condition: After the injection of pentothal sodium an average difference of 7.2 mg. per hundred cubic centimeters was obtained during light anesthesia for these same subjects; in deep depression the average fell to 5.4 mg. per hundred cubic centimeters. Thus, the gradual decrease in the arteriovenous glucose difference was similar to that observed with oxygen.

COMMENT

In order to disclose the effect of light pentothal anesthesia on the cerebral arteriovenous oxygen differences of blood containing the cortical component, whether coming from the right or from the left side, the data in A and B of table 1 were subjected to further analysis. It was found that the control values in these two tables averaged 6.89 volumes per cent, which are in close agreement with previous observations.[4c] With light anesthesia the average for the arteriovenous oxygen difference of blood carrying the cortical component was 2.75 volumes per cent, and the average for the arteriovenous oxygen difference from the opposite side was much greater, 5.9 volumes per cent. For deep anesthesia an average of 2.03 volumes per cent was observed, provided the results accompanied with a great decline of blood pressure were omitted from the calculations, but if they were included the average was raised somewhat, to 2.93 volumes per cent.

The decrease in the arteriovenous oxygen difference produced by pentothal sodium confirms the observations in previous experiments with amytal, in which, however, the amount of the drug was sufficient only to place the subject in light depression. Dameshek, Myerson and Loman [9] reported that the average arteriovenous oxygen difference of 6.4 volumes per cent fell to 5.7 volumes per cent after the administration of sodium amytal. Confirming this small, but significant, decrease are the unpublished results of Dr. F. A. Hale and one of us (H. E. H.), who found an average arteriovenous oxygen difference of 5.8 volumes per cent after the intravenous administration of sodium amytal. This value is lower than the average arteriovenous oxygen difference for normal man, 6.7 volumes per cent.[10] These decreases in arteriovenous

9. Dameshek, W.; Myerson, A., and Loman, J.: The Effects of Sodium Amytal on the Metabolism, Am. J. Psychiat. **91**:113-135, 1934.

10. Himwich, H. E., and Fazekas, J. F.: Cerebral Arteriovenous Oxygen Difference, Arch. Neurol. & Psychiat. **50**:546-551 (Nov.) 1943.

oxygen difference were less pronounced than those reported in the present investigation, chiefly because in the previous work consideration was not given to the anatomic arrangement in the cerebral venous return or to the resulting discrepancies between the arteriovenous oxygen differences on the two sides during light anesthesia. All results were, therefore, averaged instead of presenting the effect on the cerebral component separately.

Schmidt, Kety and Pennes [11] reported that pentothal produced no consistent change in the cerebral arteriovenous oxygen difference in the monkey. If the discrepancy between the results obtained in the monkey and in man is not due to a species difference, three other reasons, based on the difference in experimental conditions, may be suggested. First, the control values of Schmidt and co-workers were made during light barbiturate anesthesia, and the present observations disclosed that under this condition the cortical component is depressed. Second, the blood of the right and of the left internal jugular vein were mixed in a common tube before the collection of the blood. To understand how this mixture cloaks the effect of pentothal on the cortical component, it is necessary to analyze the results for the patients (table 1 C) in whom both internal jugular veins carried the same kind of blood, because in these men the samples of blood were identical as the mixture of the blood took place within the cranial cavity. The average for the controls (table 1 C) was 7.62 volumes per cent. The average for patients under light anesthesia was 6.81 volumes per cent, a difference which is not significant. Thus, a mixture of the blood of the two internal jugular veins may explain, in part, the failure of the arteriovenous oxygen differences to decrease in the experiment on the monkeys. Finally, the average for the observations made on patients in deep anesthesia was 2.47 volumes per cent when the blood pressure was relatively consistent, but the value rose to 5.87 volumes per cent for those experiments in which the blood pressure began to fail. Thus, it is possible that the results of Schmidt and co-workers, which were obtained from monkeys in deepest anesthesia, revealed this type of secondary increase.

In our experiments, there may have been two causes for the greater depression of arteriovenous oxygen difference on one side: Either the blood passes through the cerebral hemispheres faster than in the lower parts of the brain, or the metabolism of the cerebral cortex is depressed more than that of the subcortex. Though we do not possess data on the effect of pentothal sodium on the cerebral blood flow of our patients,

11. Schmidt, C. F.; Kety, S. S., and Pennes, H. H.: Gaseous Metabolism of the Brain of the Monkey, Am. J. Physiol. **143**:33-52, 1945.

we know that in the monkey [11] and in the dog [12] pentothal sodium diminishes the volume of blood passing through the brain. It is also probable that the cerebral blood flow of our patients was diminished, for the systolic pressure fell from 5 to 50 mm. below the control values during our observations on the various patients, and a lowered blood pressure curbs cerebral flow. It would not seem likely, therefore, that the blood flow is accelerated in the cerebral hemispheres. If the cerebral blood flow is slowed, then a fall in the arteriovenous oxygen difference indicates a depression of cerebral oxidation. To obtain a final answer, it is necessary to determine the effect of pentothal sodium on blood flow through each internal jugular vein, and this will be our next task.[13]

These results yield a functional corroboration for the anatomic observation [4a, b] of an asymmetric venous return from the cerebral hemispheres and from the basal ganglia for 9 of 12 patients. The relatively large percentage of subjects, 25 per cent, with an approximately equal distribution of cortical blood in the two internal jugular veins may be ascribed in part to the sampling of a small, and hence not representative, number of patients. It must also be remembered that there are two ways in which the blood of the superior longitudinal sinus may appear in both internal jugular veins: One is comparatively rare, through a torcular Herophili; in the other the branches of the superior longitudinal sinus divide its blood approximately equally between the right and the left lateral sinus.

All the data presented indicate that in the lighter stages of anesthesia the oxidations in the cerebral hemispheres are more depressed than those of the other portions of the brain and that this depression is a progressively descending phenomenon which may finally involve the entire organ. The persistent effect on the cerebral hemispheres is in accordance with the well known decorticating action of the barbiturates. But that the metabolic retardation is not limited to the cortex is shown by the impairment of the arterial oxygen, which becomes especially pronounced when depression of the medulla oblongata takes place during deep anesthesia. Then anoxic anoxia is superimposed on the histotoxic

12. Homburger, E. G.; Himwich, W. A.; Maresca, R., and Himwich, H. E.: Effect of Pentothal Anesthesia on Canine Cerebral Cortex, Am. J. Physiol., to be published.

13. Since this investigation was submitted for publication, we have been able to show that during pentothal anesthesia cerebral blood flow is slowed and that the slowing is greater in the cerebral hemispheres than in the lower portions of the brain. It was further demonstrated that cerebral metabolic rate was diminished during pentothal narcosis and that the diminution exhibited a definite pattern, the cortical oxidations being depressed earlier and more profoundly than those of the rest of the brain (Himwich, W. A.; Homburger, E.; Maresca, R., and Himwich, H. E.: Brain Metabolism in Unanesthetized and Anesthetized Man, Federation Proc. **5**:47, 1946).

anoxic action of the barbiturate, as the function of the respiratory center is impaired because of its metabolic depression. This type of medullary depression does not include temporary inhibition of the respiratory center, which can occur at any time in the course of pentothal anesthesia if the rate of intravenous injection is rapid.

When respiratory inhibition occurs during the lighter stages of anesthesia, it is not directly referable to depression of medullary oxidations but may be regarded as a specific effect on the respiratory center, and in the lighter stages it is transitory. Tidal exchange becomes progressively diminished with deepening anesthesia, and this phenomenon is the result of the withdrawal of metabolic support. The consistent diminution in the arterial oxygen content demonstrates the progressive inhibition of medullary oxidations. Thus, a distinction must be drawn between the two effects of barbiturate on the nerve tissue: (1) a direct, specific depression exerted particularly on visceral nuclei, an action which is not necessarily proportional to the metabolic depression, and (2) the withdrawal of the metabolic support necessary to maintain nerve function.

In terms of blood gases, an inequality in arteriovenous oxygen differences between the right and the left side indicates in most patients that the cerebral hemispheres are depressed more than other parts of the brain, a condition designated in the present report as light anesthesia. When not only the cerebral hemispheres but the basal ganglia are included in the depression, deep anesthesia is observed as the arteriovenous oxygen differences become equal, within the experimental error, on the two sides. This deep depression may be progressive and proceed through the midbrain to the medulla oblongata.

SUMMARY AND CONCLUSION

In this investigation on the pattern of the action of pentothal sodium on the brain, it was possible to show that the cerebral hemispheres are the areas first involved in the depressant action of this drug, because of the peculiarities of the anatomic venous cerebral return, which in the majority of patients directs most of the blood from the cerebral hemispheres either to the right or to the left internal jugular vein and a major portion of the blood from the basal ganglia to the opposite vein. A total of 36 observations were made on 12 subjects under pentothal anesthesia. Of 22 observations, made at the lighter levels of anesthesia, the results may be divided into two groups: In 9 of the subjects the arteriovenous difference on one side was more depressed than that on the opposite side, and in the 3 remaining patients the arteriovenous differences were similar on the two sides. Further evidence supporting the differences between the values for the right and the left internal jugular vein is obtained from the data for glucose and lactate, for in the same 3 patients

in which the arteriovenous oxygen differences were always within the experimental error the arteriovenous glucose and arteriovenous lactate differences exhibited a similar agreement, while in the other 9 patients the paired results did not show a similar precise concordance. With deeper anesthesia the subcortical parts became more involved, and the paired arteriovenous oxygen differences for the two sides were greatly depressed and within the experimental error in all but 2 of 14 observations. These results indicate that oxidation is not decreased to the same extent in all parts of the brain at the lighter levels of barbiturate anesthesia but that the cerebral hemispheres are the areas of the brain preponderantly involved in the depressant action of the drug. The other parts of the brain gradually suffer an increasing inhibition of oxidation as the deep levels of pentothal anesthesia are produced.

Albany Medical College (3).

EFFECTS OF ANTIBIOTIC SUBSTANCES ON THE CENTRAL NERVOUS SYSTEM

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THERE HAS been a singular dearth of experimental studies on the effects of penicillin and other antibiotic substances on the physiologic processes of the nervous system. The lack of clinical evidence of neural toxicity when penicillin is administered systemically or intrathecally is astonishing when the antibacterial potency of the drug is considered. However, the observation of convulsive manifestations following intraventricular administration [1] led to a study of the effects of antibiotic substances on the nervous system. This report concerns the neuropharmacodynamics of penicillin,[1] streptomycin, clavacin, actinomycin and streptothricin. An attempt was made to test the effects of aspergillic acid on the brain, but its relative insolubility in water made the experiment unsatisfactory.

PENICILLIN [2]

Penicillin, one of the antibiotic principles obtained from Penicillium notatum, is the best known and one of the most powerful of the bactericidal substances of microbial origin.

From the Division of Neurological Surgery and the Otho S. A. Sprague Foundation, the University of Chicago.

The work described in this paper was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Chicago.

1. Johnson, H. C., and Walker, A. E.: Intraventricular Penicillin: A Note of Warning, J. A. M. A. **127**:217-219 (Jan. 27) 1945.

2. The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for Experimental Investigations, recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

Dr. D. F. Robertson, of Merck & Co., Inc., supplied the streptothricin; Dr. G. W. Rake, of the Squibb Institute for Medical Research, the aspergillic acid; Dr. G. M. Everett, of Abbott Laboratories, the streptomycin and clavacin, and Dr. S. A. Waksman, State of New Jersey Agricultural Experimental Station, the actinomycin.

When administered systemically it apparently does not reach the central nervous system in appreciable amounts. However, there is evidence that in the presence of meningeal irritation the pencillin may pass into the spinal fluid in increased amounts and may reach concentrations sufficiently high to kill the more sensitive bacteria. There appears to be little clinical evidence, however, that penicillin given systemically induces alteration in nervous function. In view of the fact that convulsive manifestations were noted when penicillin was applied to the cerebral cortex,[3] electroencephalographic studies were made on a series of 51 patients who were receiving penicillin therapy for some condition other than a primary neurologic one. The records of only 20 patients were normal at all times; the other 31 patients showed abnormalities on one or more examinations. Control records taken before and after penicillin therapy were available for 18 of these 31 patients. In 4 patients having control records before and after the therapy, there was evidence of increased electrical activity during the administration of the drug, with normal records both before and after the therapy. On two occasions during the course of penicillin therapy, 1 of these patients showed evidence in the electroencephalogram of abortive or subclinical epileptic "seizures" which were not seen in any of the control records. Seven patients showing increased activity in the electroencephalogram during the period of penicillin therapy had a similar pattern after the withdrawal of therapy. Unfortunately, pretreatment records were not made. Six of these 7 patients were children between 5 and 14 years of age; their records suggested a convulsive diathesis. Four patients with control records only after therapy showed pronounced diminution of electrical activity after withdrawal of the drug. For 2 patients the electrical activity of the brain was less during administration of the drug than in the control records. On the basis of these observations it appears that subclinical alterations in cerebral function may occur during the time of administration of penicillin in somewhat more than 50 per cent of cases (figs. 1, 2, 3 and 4).

Although usually only subclinical effects are present during systemic administration, overt clinical manifestations may develop when the drug is applied directly to the central nervous system, either by intrathecal injection or by direct application to the brain. After lumbar intrathecal injection the mild meningeal irritation, manifested by pleocytosis and increased protein in the spinal fluid, is well known. That neural complications may develop is not so well recognized. In the monkey the lumbar injection of 20,000 units of penicillin causes

3. Walker, A. E., and Johnson, H. C.: Convulsive Factor in Commercial Penicillin, Arch. Surg. **50**:69-73 (Feb.) 1945.

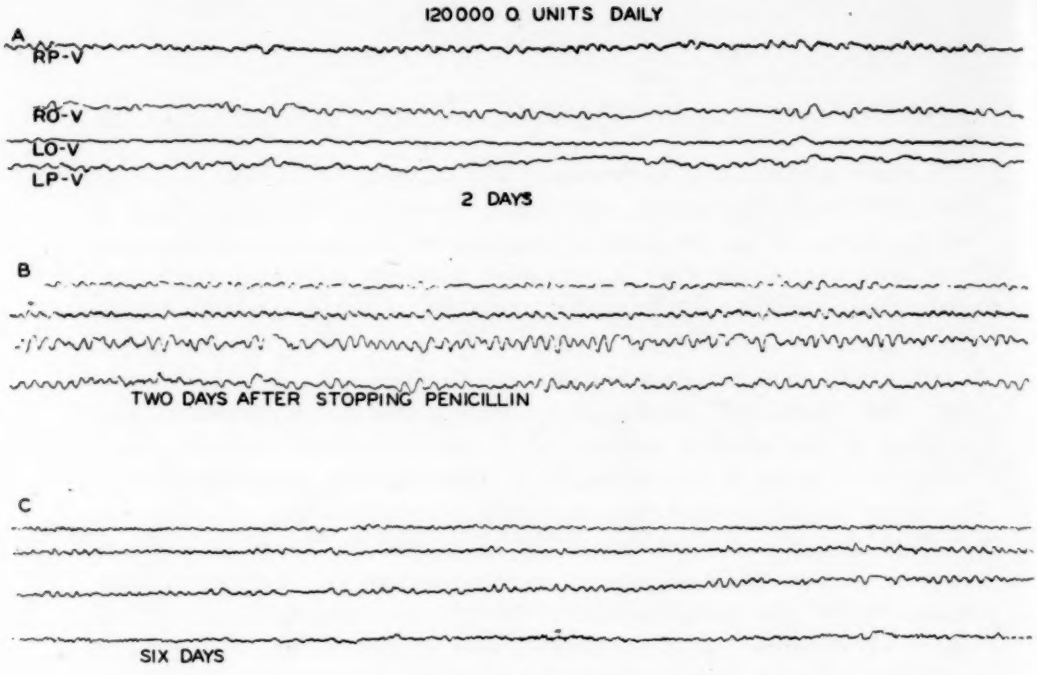

Fig. 1.—Electroencephalograms of a woman aged 19 who had a wound infection following thoracolumbar sympathectomy for high blood pressure.

(*A*) The record shows considerable abnormal activity two days after penicillin therapy was started. (*B*) Fifteen days later, or two days after stopping penicillin, the record shows substantial increase of abnormal activity in all areas. Much of it appears as a slowed alpha wave (about 7 cycles per second) but there is considerable energy of both faster and slower frequency than the alpha activity. (*C*) A tracing taken six days after penicillin treatment was stopped shows substantial decrease of abnormal activity.

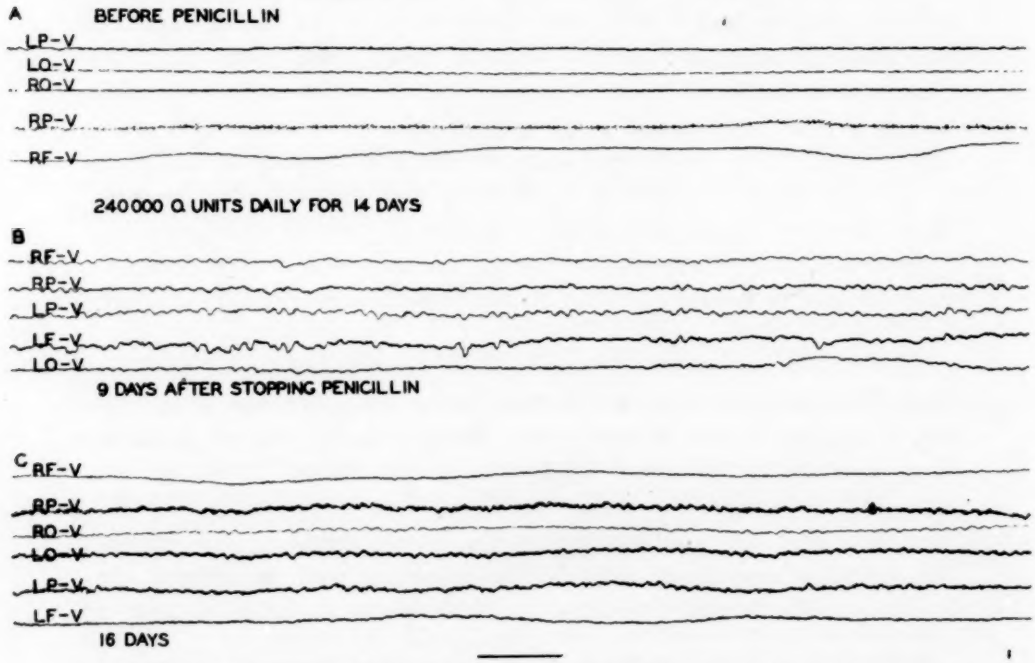

Fig. 2.—Electroencephalograms of a woman aged 36 with an actinomycotic infection of the chest and spine.

A, a tracing taken before penicillin therapy was started, shows only a little muscular activity in the right parietal lead. *B* is a record taken nine days after administration of penicillin for fourteen days; *C* is a tracing taken sixteen days after penicillin therapy was stopped.

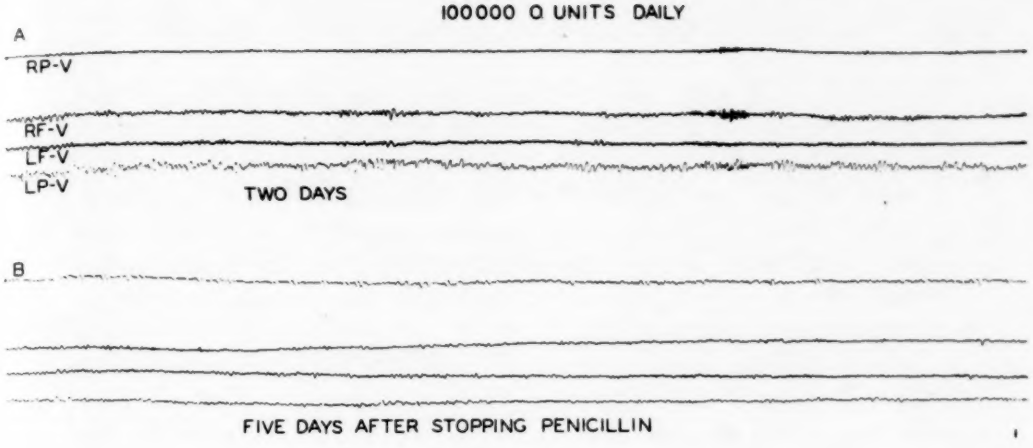

Fig. 3.—Electroencephalogram of a woman aged 35 with an infection of the urinary tract. *A*, a record taken two days after penicillin therapy was started, shows considerable fast, beta-like activity, which at times is sharp and spiky. *B*, a record taken five days after penicillin therapy was stopped, shows substantial decrease in the fast activity.

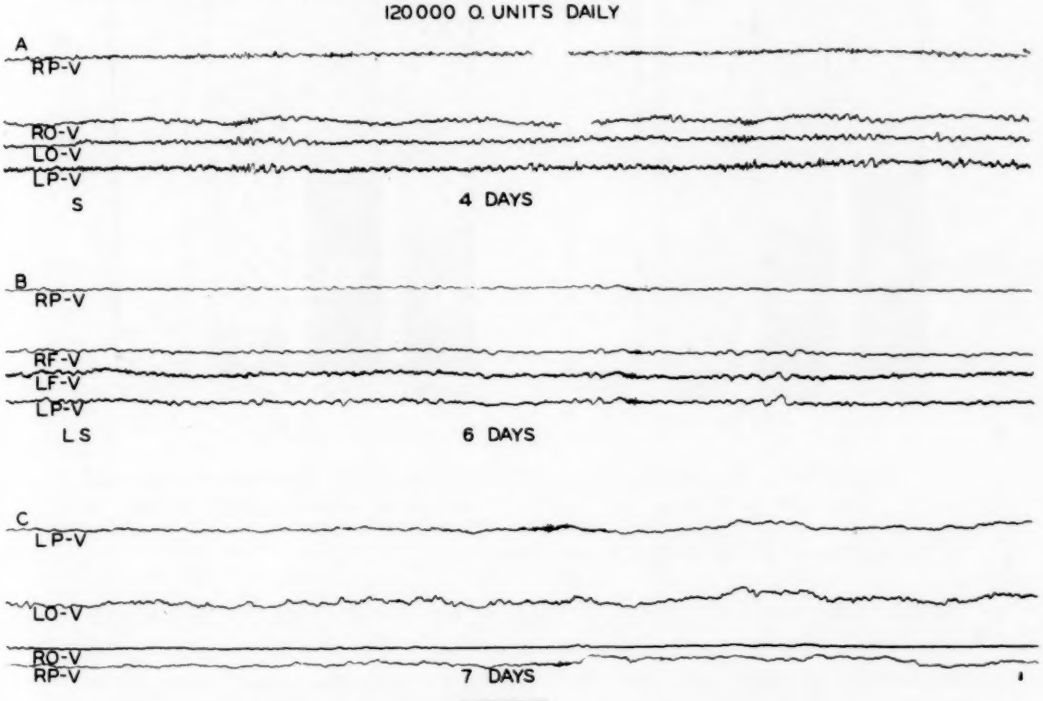

Fig. 4.—*A*, electroencephalogram of a man aged 38 who had an infection of the urinary tract after removal of a stone from the renal pelvis. The record, taken four days after penicillin therapy was started shows fast activity in all leads.

B, record of a woman aged 24 who had an abscess in a laparotomy wound, taken six days after treatment with penicillin was started. Another record, taken three months after penicillin therapy was stopped, did not look very different. The patient was thought probably to have an epileptic diathesis.

C, electroencephalogram of a 9 year old girl who broke her arm six days before penicillin therapy was started. The record was taken seven days after administration of penicillin was begun. The irregularities were considered questionably epileptic.

the animal to inspect, rub and then vigorously scratch his tail and perianal region for a half-hour or more after the injection. After a few hours the animal appears normal again. In man, however, a number of cases of sacral radiculitis have been reported to follow intrathecal penicillin therapy.[4] Paresthesias, urinary retention and sensory and motor disturbances in the lower extremities have characterized the clinical picture. Fortunately, the radiculitis has usually cleared up in a few weeks or months.

Probably because the diffusion of penicillin from the lumbar subarachnoid space is slow, alterations in cerebral function have not been seen even after the injection of enormous amounts of penicillin by

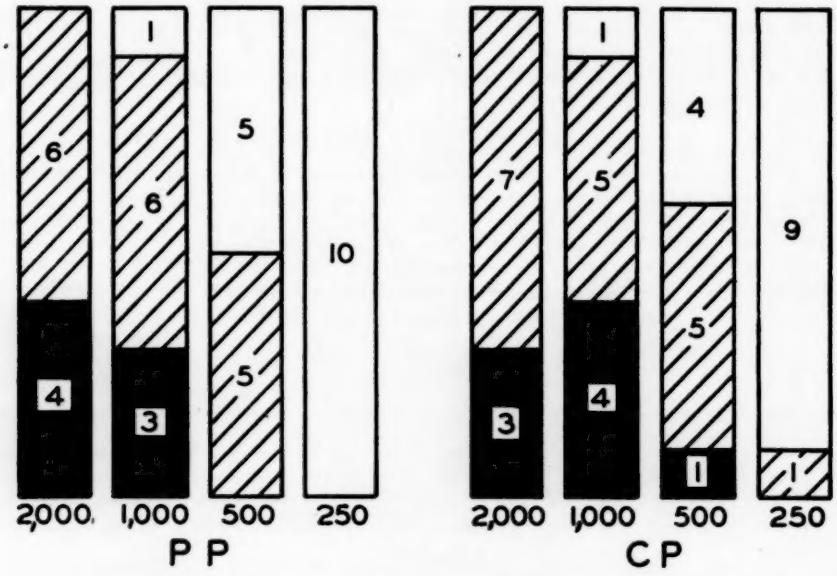

Fig. 5.—Histograms showing the convulsive responses (generalized fits, solid black; unilateral twitching, lined, and no convulsive manifestation, white) to the intracortical injection of crystalline (*P P*) and commercial (*C P*) penicillin in doses of from 250 to 2,000 Oxford units.

lumbar puncture. However, if large doses of the drug are introduced into the cisterna magna, serious sequelae may result. In both the experimental animal and man convulsive seizures, coma, and even death, may occur. In the monkey 10,000 units of penicillin may induce these complications; in man 40,000 units has been known to produce them.[5] In

4. Sweet, L. K.; Dumoff-Stanley, E.; Dowling, H. F., and Lepper, M. H.: The Treatment of Pneumococcic Meningitis with Penicillin, J. A. M. A. **127**: 263-267 (Feb. 3) 1945.

5. Neyman, C. A.; Heilbrunn, G., and Youmans, G. P.: Experiments in the Treatment of Dementia Paralytica with Penicillin, J. A. M. A. **128**:433-434 (June 9) 1945.

experimental animals the minimal convulsive dose of penicillin has been determined. In the dog and monkey approximately 500 Oxford units of penicillin applied to the cerebral cortex is sufficient to induce convulsive manifestations, which initially consist of clonic spasms of the

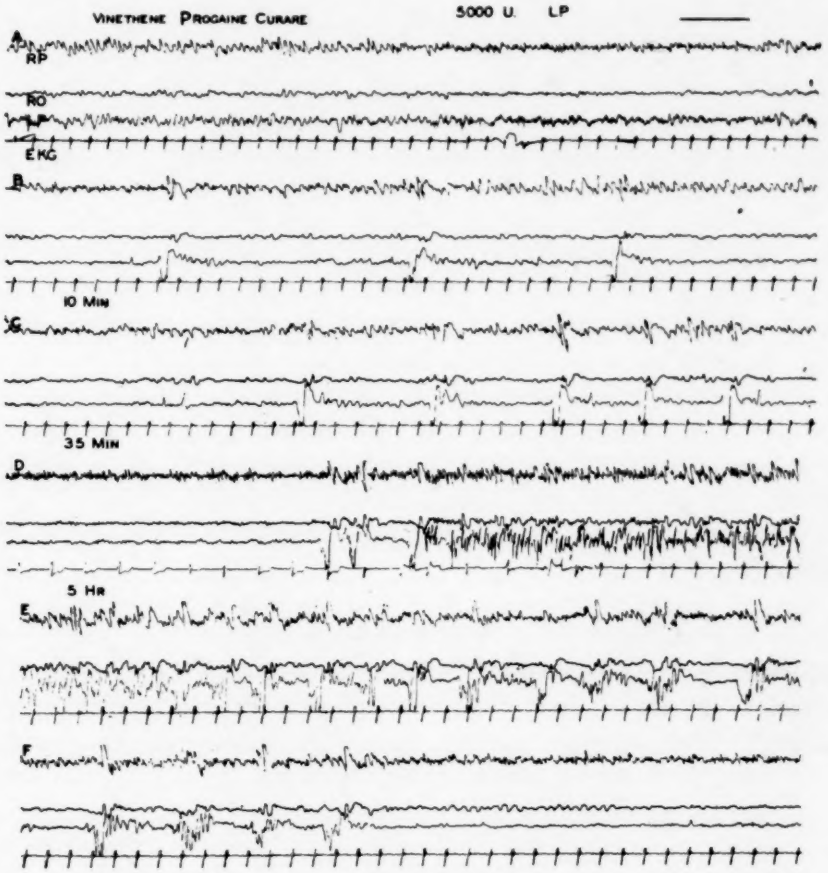

Fig. 6.—Electrocorticograms taken from electrodes screwed into the calvaria of a cat prepared with vinethene anesthesia. The scalp was procainized, and the animal was given curare and artificially aerated.

A, control record. *R. P* indicates the right frontoparietal lead; *R O*, the right parieto-occipital lead; *L P* the left frontoparietal lead, and *EKG* the electrocardiogram.

B, record taken ten minutes after an injection of 5,000 Oxford units of penicillin in the subdural space of the left parietal region. The spikes are particularly prominent in the left frontoparietal lead.

C, record taken thirty-five minutes after the injection, showing the spikes more frequent and larger in the right-sided leads.

D, *E* and *F*, records taken five hours after the injection. These records are continuous, showing the electroencephalographic manifestations of a generalized convulsion.

An interval of one second is indicated by the horizontal line in the upper right corner; just below the first tracing at the right side is a calibration of 60 microvolts.

contralateral extremities but later usually involve all limbs in the manner of a generalized epileptic seizure. In man, the convulsive threshold, as determined by as yet inadequate studies, appears to be considerably higher. These toxic manifestations are not due to impurities in the penicillin, for pure crystalline penicillin induces the attacks (fig. 5). In the experimental animal, monkey, cat or dog, the convulsive phenomena usually spontaneously decrease and disappear in eight to ten hours. Occasionally the animal passes into coma and dies. Anticonvulsant medication, such as administration of phenobarbital, will control the attacks in experimental animals. After the spontaneous or pharmaceutically induced cessation of the seizures, the animal quickly recovers and the next day appears normal. Gross examination of the brains of animals so treated shows only a small area of brownish discoloration at the site of the injection. Microscopic studies of these lesions reveals a small granuloma, with lymphocytic infiltration practically confined to the area of the injection.

It may, then, be concluded that penicillin when applied to the central nervous system in adequate amounts (fortunately, far above therapeutic requirements) will induce convulsive manifestations, which usually are of a temporary nature. These clinical fits are accompanied with the electroencephalographic manifestations which characterize epileptic attacks (fig. 6).

STREPTOMYCIN

Streptomycin, a bactericidal substance obtained from Actinomyces griseus, is the least toxic of the antibiotic derivatives of the actinomycetes.[6] It is effective against gram-negative bacteria in general, as well as against certain gram-positive organisma.

Knowledge of the effects of streptomycin on the nervous system is based on experimental studies on monkeys and cats. After 10,000 units of streptomycin was injected, without technical difficulty, into the cisterna magna of a monkey, within two minutes the animal became unsteady and so ataxic that standing or sitting was impossible. A spontaneous nystagmus and a fine tremor of the head developed. The ataxia persisted for several hours, but the following morning the animal appeared normal. In another animal the injection of 5,000 units of streptomycin induced the same phenomena. When 2,500 units was injected in another monkey, the animal sat quietly humped up in its cage for several hours. An intracisternal injection of 1,250 units of streptomycin in a monkey caused no apparent abnormality. The

6. Waksman, S. A.; Horning, E. S., and Spencer, E. L.: Two Antagonistic Fungi, Aspergillus Fumigatus and Aspergillus Clavatus, and Their Antibiotic Substances, J. Bact. **45**:233-248 (March) 1943.

injection of 1,250 units of streptomycin in the parietal cortex of each of 10 monkeys induced in 2 animals slow, awkward waving movements of the upper extremity contralateral to the site of injection and slow movement of retraction of the corner of the mouth. These phenomena began approximately one-half hour after injection, lasted for one hour and graduallly subsided. When the experiment was repeated on another day, 4 of the 10 monkeys exhibited the peculiar slow movements of the

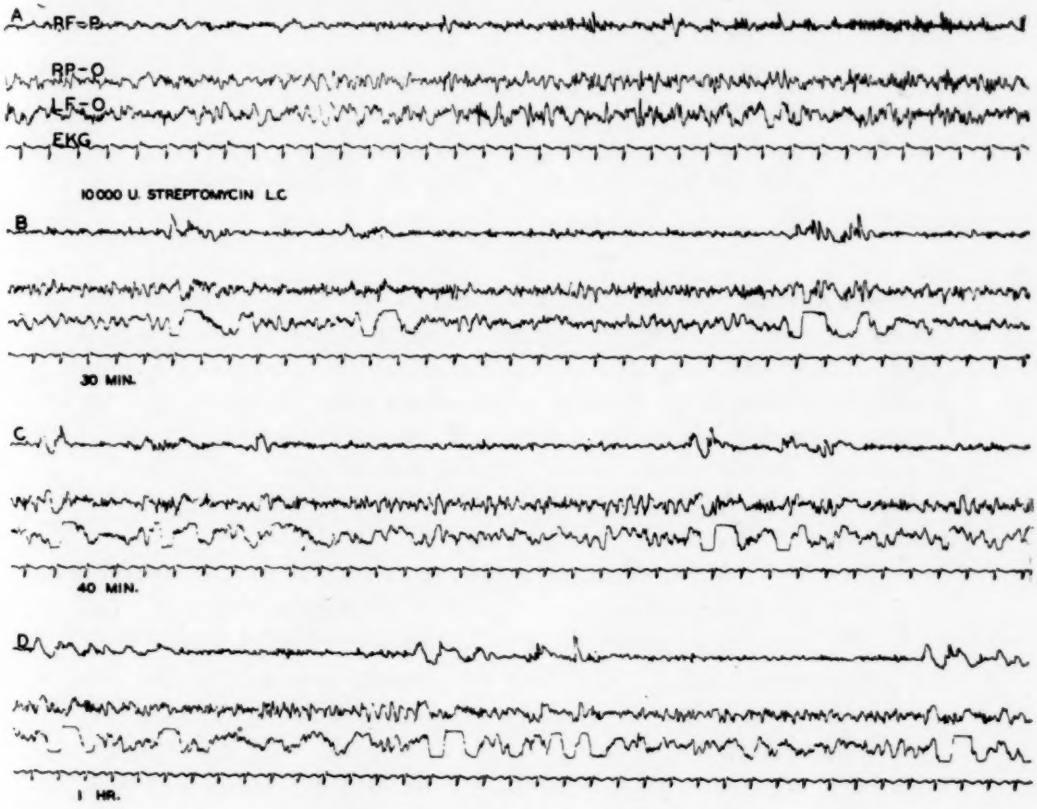

Fig. 7.—A series of electroencephalograms taken on a monkey prepared with procaine anesthesia, curarized and artifically aerated. The leads were as follows: *RF-P,* right frontal and parietal leads; *LF-O,* left frontal and occipital leads *EKG,* electrocardiogram taken from needle electrodes in the muscles of the two upper extremities. The animal had had 25,000 units of penicillin implanted in the right frontal area six weeks before this experiment. Probably the spiky, irregular hyperactivity of the cerebral cortex is due to this implant. *A,* control record; *B,* record taken thirty minutes after intracortical injection of 10,000 units of streptomycin into the left central (*LC*) region, showing more pronounced spikes and humps; *C,* record taken forty minutes after injection, with the humps and spikes still apparent; *D,* record one hour after the injection. The irregular activity with spikes and humps, particularly on the left side, is prominent.

The horizontal line at the base indicates an interval of one second; the vertical line at the right, a calibration of 60 microvolts.

contralateral extremities for one to two hours. The following day all the animals appeared normal. Gross examination of the brain of these animals showed the same minor changes as in the brain into which penicillin had been injected. Electroencephalograms taken after the application of 5,000 to 10,000 units of streptomycin to the cerebral cortex of 3 cats and 3 monkeys showed waves or humps, lasting one-half second and occasional spikes from the leads on the side of injection. In some animals, particularly in the monkeys, the cortical activity over the entire brain decreased and remained at a low level for one and a half to three hours (fig. 7).

It is concluded that streptomycin applied to the central nervous system will induce mild convulsive manifestations of a temporary nature. The clinical and electroencephalographic manifestations are less severe than those produced by equivalent (at least in terms of units) doses of penicillin.

STREPTOTHRICIN

Streptothricin, an antibiotic substance isolated by Waksman and Woodruff [7] from Actinomyces lavendulae, has a pronounced bactericidal effect on gram-negative and on some gram-positive bacteria. Unfortunately, the drug is fairly toxic when administered systemically. Its local application to the cerebral cortex of the cat and monkey in doses of 5,000 to 10,000 units induced clinical and electroencephalographic evidence of convulsive phenomena, which persisted for two to three hours and then spontaneously ceased (fig. 8).

In 2 monkeys, after intracortical injection of 5,000 units of streptothricin the convulsive phenomena continued to be manifested as twitching of the side of the face and the ipsilateral upper extremity for more than two weeks, at the end of which time the animals were killed. Beneath the site of injection an area of encephalomalacia was present, with numerous petechial hemorrhages. It would appear, then, that streptothricin not only is a convulsive agent but in some cases causes a necrobiotic reaction in the brain.

ACTINOMYCIN

Actinomycin, a crystalline substance, isolated by Waksman and Woodruff [7] from Actinomyces antibioticus, is a powerful bacteriostatic agent but is highly toxic when given systemically to experimental animals.

The effect of actinomycin on the central nervous system has been studied in 11 monkeys and 2 cats. In 1 monkey 1 mg. of actinomycin

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7. Waksman, S. A., and Woodruff, H. B.: Selective Antibiotic Action of Various Substances of Microbial Origin, J. Bact. **44**:373-384 (Sept.) 1942.

(equivalent to about 1 mg. of crystalline penicillin) dissolved in isotonic solution of sodium chloride was injected into the cisterna magna. The animal appeared normal until about nine hours later, when it became noisy and restless. If it was disturbed, fascicular twitchings were noted in the muscles of the extremities. Twenty-two hours after the injection the animal was noisier, appeared apprehensive and was lying down in the cage. The fasciculations of the limb musculature were more violent, and local and generalized tonic spasms developed. Twenty-eight hours after the injection the animal died. The brain appeared grossly normal,

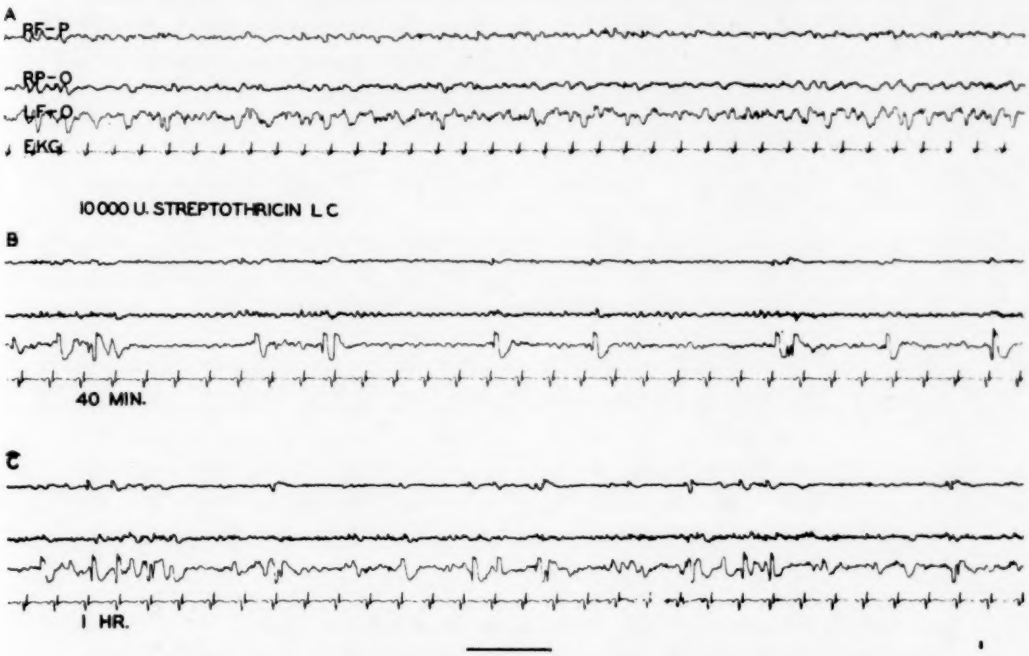

Fig. 8.—Electroencephalograms of a cat prepared with procaine anesthesia, curarized and artificially aerated. The leads are as follows *RF-P*, right frontal and parietal leads; *RP-O*, right parietal and occipital leads; *LF-O*, left frontal and occipital leads; *EKG*, electrocardiogram taken from needle electrodes in the muscles of the two upper extremities.

A control record; *B*, record taken forty minutes after injection of 10,000 units of streptothricin in the left central region (*LC*), showing the generalized decreased cortical activity and spikes, which are more pronounced on the left side than on the right; *C*, record one hour after the injection. The cortical activity is returning, but the spikes are still present.

The horizontal line at the base represents an interval of one second; the vertical line at the right, a calibration of 60 microvolts.

but histologic examination showed a severe meningitis, with leukocytic infiltration and neuronal changes in the cerebral cortex and brain stem.

In a series of 10 monkeys, 1 mg. of actinomycin was injected into the left parietal region of the cerebral cortex. The animals appeared well on the day of injection, but the next day all were apathetic, akinetic

and anorexic. On the second day spasms of the forelimbs were noted in several animals. On the morning of the third day 3 of the animals were dead. The others were prostrated; 6 of them had right-sided clonic fits, lasting two to three minutes and occasionally developing into generalized convulsions. One of the 6 animals had right hemiplegia. Three of these animals were killed. Of the 4 remaining monkeys, 1 died on the fifth day, 1 on the sixth day and 1 on the seventh day, and the last animal was killed on that day. The brains of all ten animals presented similar lesions. The left cerebral hemisphere was swollen, and about the point of injection was a discolored area, varying from a few millimeters to 2 or 3 cm. in diameter. Sections of the brain showed an area of necrosis below the point of injection, with pronounced edema and perivascular hemorrhages in the surrounding brain.

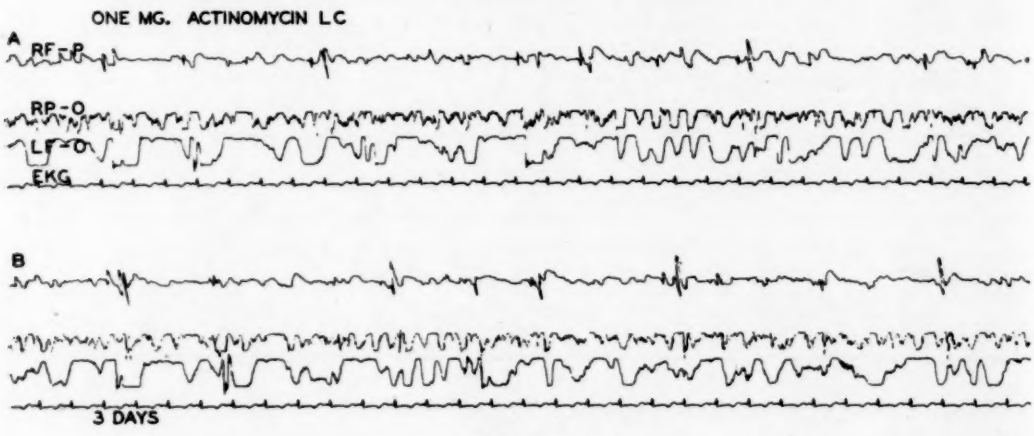

Fig. 9.—Electroencephalograms taken from a monkey three days after the intracortical injection of 1 mg. of actinomycin in the left central (*LC*) region. The slow waves in the left leads and spiky, irregular activity in the right leads are quite evident. The leads are as follows: *RF-P*, right frontal and parietal leads; *LF-O*, left frontal and occipital leads; *RP-O*, right parietal and occipital leads; *EKG*, electrocardiogram taken from needle electrodes in the muscles of the two upper extremities. The horizontal line at the base indicates an interval of one second; the vertical line at the right, a calibration of 60 microvolts.

Electroencephalograms made immediately after the application of actinomycin to the cerebral cortex of two cats showed only a few spikes in the leads from the side of the brain in which the injection was made. Records made of 1 monkey three days after the intracortical injection of 1 mg. of actinomycin showed conspicuous increase in electrical activity with irregular spikes (fig. 9).

It is concluded that actinomycin produces a severe necrobiotic reaction when applied to the cerebral cortex, manifested clinically by apathy, convulsive phenomena and death. The drug appears rather toxic even when given in relatively small doses into the cisterna magna.

CLAVACIN

Clavacin, an antibiotic substance derived from Aspergillus clavatus, is bactericidal to both gram-positive and gram-negative bacteria, but it is highly toxic when administered systemically.

Clavacin in granular form applied to the cerebral cortex even in relatively large amounts produces no clinical or electroencephalographic

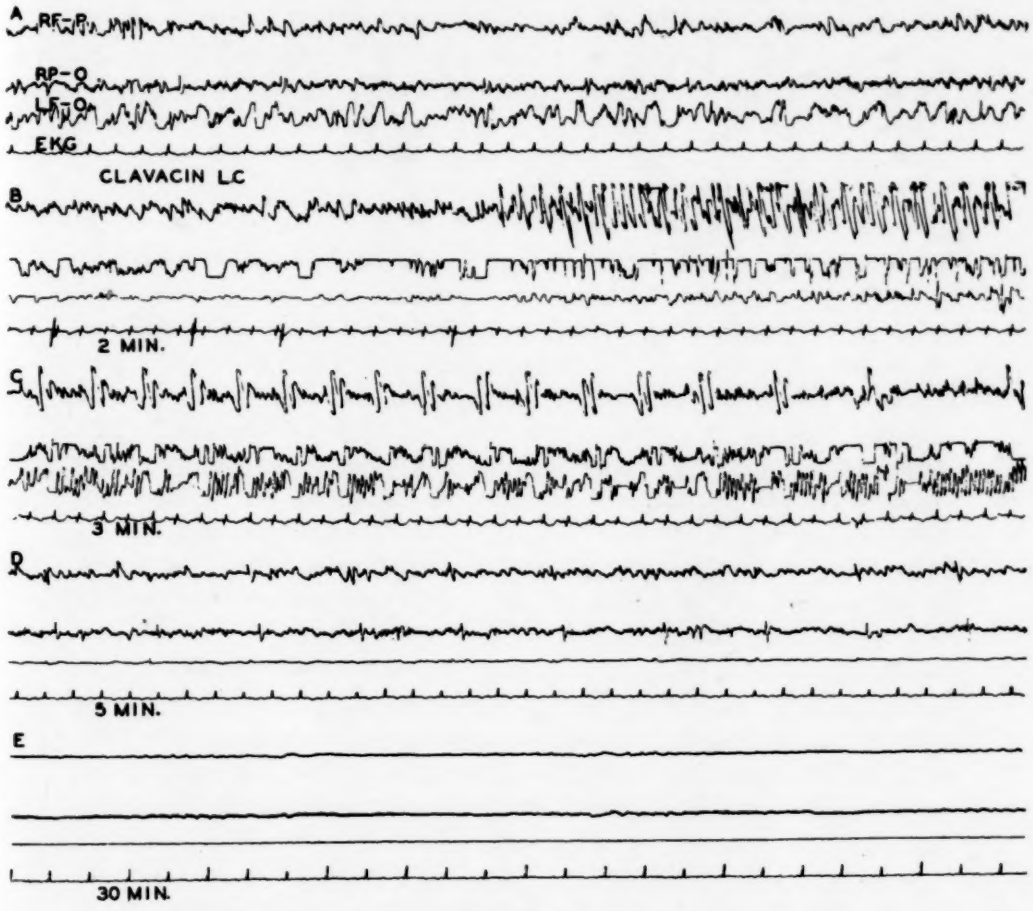

Fig. 10.—Electroencephalograms taken from a cat prepared with procaine anesthesia, curarized and artificially aerated. The leads are as follow: *RF-P*, right frontal and parietal leads; *RP-O*, right parietal and occipital leads; *LF-O*, left frontal and occipital leads, *EKG*, electrocardiogram taken from muscles electrodes inserted in the muscles of both upper extremities.

A, control record; *B*, record two minutes after the injection of 1 mg. of clavacin in the left central (*LC*) region (the convulsive activity is pronounced); *C*, record three minutes after the injection, showing a generalized seizure; *D*, record five minutes after the injection, with decreasing cortical activity and only occasional spikes; *E*, record thirty minutes after the injection, with the cortical activity abolished.

The horizontal line at the base indicates an interval of one second; the vertical one at the right, a calibration of 60 microvolts.

abnormalities. If, however, the clavacin is dissolved in water by heating and is then applied to the parietal cortex in doses of 5 to 10 mg., pronounced changes occur in the electroencephalogram (fig. 10). The normal electrical activity of the cerebral cortex is rapidly dampened, so that twenty minutes after the application of the drug the record is absolutely flat. In 1 cat, after application of 10 mg. of clavacin dissolved in 0.5 cc. of isotonic solution of sodium chloride severe convulsive phenomena appeared in the electroencephalogram, and within two minutes a major convulsion was recorded electroencephalographically. After this attack the electrical activity on the side of the injection decreased, although diphasic spikes were still present in the leads from the other side. After ten minutes the record was flat.

COMMENT

All the antibiotic substances so far examined have shown convulsant propensities when directly appiied to the central nervous system in large doses. The intensity of the epileptogenic factor varied with the drug being tested. Comparison of their convulsant effect is difficult, because their antibiotic activities are not equivalent, penicillin being effective largely against gram-positive organisms and streptomycin against gram-negative bacteria. Until the active principles are isolated in chemically pure form, a valid comparison of the convulsant factors is impossible. It seems reasonable to state, however, that penicillin and streptomycin may be applied to the central nervous system without toxic effects in doses far above an adequate antibiotic concentration, whereas streptothricin, actinomycin and clavacin appear to produce severe toxic effects in concentrations little, if at all, above therapeutic levels. It would seem then that the latter antibiotic substances would not be acceptable for clinical use in the central nervous system even if they had no systemic toxic effects. The other drugs, from the standpoint of convulsive effects, would appear to be acceptable for therapeutic application to the central nervous system in antibiotic concentrations. All, however, may give rise to convulsive phenomena if large doses are administered. The margin between the therapeutic concentration and the convulsive threshold is, however, so great that with reasonable care the toxic effects should be avoidable.

SUMMARY

Clinical and experimental studies indicate that penicillin may produce convulsive manifestations. During systemic administration for conditions other than primary ones of the central nervous system, the electroencephalogram was found to be abnormal in more than 60 per cent of a series of 51 patients. Control records taken before and after penicillin therapy usually showed normal tracings. Large doses of penicillin

injected intrathecally in man or monkey may give rise to convulsions, followed in some cases by coma and death. The application of as little as 500 international units to the cerebral cortex of the macaque monkey may induce epileptic attacks.

Streptomycin in cats and monkeys applied to the cerebral cortex in doses of 1,250 units induced convulsive manifestations in 30 per cent of the animals. Electroencephalographic records at such times showed slow waves and spikes, with subsequent decrease of cortical activity lasting for one and one-half to three hours. Cisternal injection in the monkey of 2,500 units of streptomycin induced signs of severe cerebellar dysfunction.

Streptothricin applied to the parietal cerebral cortex in doses of 5,000 to 10,000 units produced clinical and electroencephalographic convulsive manifestations. Although these phenomena usually disappeared spontaneously in two to three hours, in 2 monkeys they persisted for two weeks. At necropsy the brains of these animals showed extensive softenings with perivascular petechial hemorrhages.

Actinomycin injected into the cerebral cortex or the cisterna magna in a dose of 1 mg. after a latent period of nine hours produced severe prostration, fasciculations and convulsions, with death in one to seven days. At the site of injection into the cerebral cortex a severe necrobiotic reaction with edema and petechial hemorrhages was found.

Clavacin when injected into the cerebral cortex in doses of 5 to 10 mg. induced clinical and electroencephalographic manifestations of convulsive phenomena with a marked decrease in spontaneous cerebral activity.

There appears to be a wide margin of safety between the antibiotic concentration of penicillin and streptomycin and the convulsive threshold for those drugs. Such does not appear to be the case for streptothricin, clavacin or actinomycin. Although penicillin has few toxic reactions, if it is given in excessive amounts in the cerebrospinal fluid, severe neural sequelae in the form of radiculitis or convulsions may develop.

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ABNORMAL DELAY OF VISUAL PERCEPTION

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THE NEED for discovering a nervous disorder as early as possible is obvious. The diagnostic method to be described here utilizes a peculiar visual phenomenon which makes possible recognition of minute unilateral delays in perception of visual impulses. It is expected that this method, which takes advantage of the high degree of sensitivity of visual reception, will promote recognition of the disturbed function of the optic nerve at an earlier state than is obtainable with the existing methods.

Fully aware of the incompleteness of my clinical investigations,[1] which began in 1942 and were interrupted by the exigencies of the war, I present the method for the purpose of further study in competent institutions.

THE PULFRICH EFFECT

The basic phenomenon is easily observed with the following simple setup: Let a pendulum (some small dark object tied to a thread) swing in front of and parallel with a light vertical background, and either squeeze one eye by an attempt at forceful closing or put a smoked glass in front of one eye. Suddenly the pendulum no longer appears to swing in a plane parallel with the background but seems to describe a horizontal circle, approaching the observer and receding behind its initial, vertical, plane. In other words, a stereoscopic, three dimensional effect is produced by an actually two dimensional movement.

An explanation of this phenomenon, first observed by an astronomer, was made and published by Pulfrich [2] (who, paradoxically, was one eyed from childhood and was thus deprived of stereoscopic vision): Reduction of the light entering one eye makes the image on this retina darker than the image on the other retina. It being accepted that of two optic impulses the weaker one is transmitted more slowly, the sensation from the eye with dimmed vision is registered in consciousness a trifle later than the sensation from the unobstructed eye. Under the

1. This investigation was supported in part by the Jennie Grogan Mendelson Memorial Fund for Ophthalmology and was carried out at the Ophthalmic Research Laboratory, Wayne University College of Medicine.

2. Pulfrich, C.: Stereoscopy in the Service of Isochromatic and Heterochromatic Photometry, Naturwissenschaften **10**:553 (June) 1922.

special experimental conditions, this time difference is transposed into a spatial difference, with resulting stereoeffect.

(A detailed description of this "Pulfrich effect" will be presented at the end of this paper.)

RATIONALE OF CLINICAL APPLICABILITY

In the original experiment, the time difference between perception of the optic impulses on the right and left sides is produced by an objective difference of illumination. The same effect may be expected to occur in spite of identical illumination for the two eyes if the transmission of the impulses between retina and visual cortex is delayed unilaterally, owing to pathologic conditions. This delay, however, may be so minute as to be below the threshold of consciousness, thus necessitating some "magnifying" procedure in order to promote its recognition. Such a procedure was developed along the following line of thought:

In normal subjects the Pulfrich effect is induced when the brightness difference for the two eyes has reached a certain magnitude. It is to be expected that the brightness difference required for the effect would be smaller for persons with an already existing "subthreshold" delay in transmission of impulses. Hence it is necessary only to design a simple quantitative method of reducing the intensity of the incident light for either eye.

DEVICE FOR CLINICAL INVESTIGATION

In a regular frame for refraction work one pair of polaroid glasses was fitted for each eye. While the polaroids adjacent to the eye were fixed in their positions, the outer polaroids could be rotated, with the angle of rotation easily measured on a scale along the circumference of the frame. The initial position of the outer polaroids was adjusted for maximal transmission of light. Rotation of either—right or left—outer polaroid resulted in gradual darkening of any desired degree, with a defined relation to the angle of rotation.

The apparatus[3] consisted of a framed square of frosted glass; an electric light behind the glass produced the illumination of the screen, in front of which, in the lower half of the field, a vertical black rod moved with constant, but variable, speed from one side of the frame to the other, to and fro. This rod was driven by an electromotor; the speed of the movement was controlled by a resistance and measured by means of a modified taxmeter checker. A fixed metal rod attached to the center of the upper frame extended vertically downward into the upper half of the field. The lengths of the fixed and of the movable rod were so adjusted that the lower rod when passing its midway position appeared to be the direct continuation of the upper rod.

This fixed rod serves two purposes: It is the fixation point for the observer, and it marks the virtual center of the apparent circle described by the moving rod when the stereoeffect becomes manifest.

3. Manufactured by the Nichols-Chase Company, Detroit.

PROCEDURE OF TESTING FOR PULFRICH EFFECT

Since a normal observer serves as the standard of comparison, the extent of darkening required to elicit the stereoeffect is determined for each eye of the investigator before the patient is examined. (This value remained amazingly constant, as recorded over a period of five months.) It is advisable to have the rotation of the movable polaroid made by an assistant, at least in the beginning, in order to avoid the pitfall of training muscle and posture sense of the rotating fingers, tending to stop the rotation always at the same position. It is also essential to proceed rather fast from the initial position of the polaroid. When the darkening proceeds at a slow pace, the threshold is "driven"; the observer is fatigued, and it becomes difficult to decide where the stereoeffect began.

The observer should be seated at such a distance from the apparatus that the two rods can be clearly recognized. For an observer with emmetropic or corrected vision a distance of approximately 6 feet (180 cm.) proved satisfactory. With myopic subjects, if no eyeglasses are worn, the distance must be reduced.

For a given brightness difference between the eyes, the Pulfrich effect becomes more intense the faster the movable rod travels through the illuminated field. There is, however, a speed limit to this intensification when fatigue and blur intervene. Hence it is important to select a speed which is favorable for an impressive stereoeffect and to keep this speed constant throughout the test.

Testing proceeds in the following steps:

1. The room is darkened, and the frosted glass is illuminated.
2. The normal observer, at the chosen distance, adjusts the outer, movable, polaroids for maximal transmission of light while looking at the illuminated screen. The numerical value of this starting position is recorded.
3. The motor is turned on and kept at convenient speed.
4. The outer polaroid of one eye is rotated until the Pulfrich effect appears. The angle of rotation is recorded and the test repeated from three to five times.

The same procedure is carried out with the other eye.

Before the patient undergoes the testing, the following factors must be determined:

1. Whether the pupils are of equal width. Although slight or even moderate, anisocoria did not seem to influence the threshold of the Pulfrich effect, a considerable pupillary difference will create such difference in retinal brightness as to influence the stereoeffect. Similarly, corneal opacities or cataract may interfere with the test.
2. Whether the patient when looking at the illuminated glass with both eyes and alternately with either eye experiences any difference of brightness sensation between his eyes. If he does, the test cannot be applied.
3. Whether the patient when looking at the screen with the rod in motion but without polaroids experiences the Pulfrich effect. There are persons who do, and from the direction of the apparent circular movement—whether clockwise or counterclockwise—the side of the transmissional delay can be determined.[4]

4. The phenomenon is explained in connection with the figure.

4. Whether the patient experiences the Pulfrich effect at all. There are not infrequently persons who, in spite of extreme brightness difference and high speed of the moving rod, fail to experience the Pulfrich effect. This failure may be caused by any of the following conditions:

(*a*) The capacity for stereopsis may be totally lacking. (In this connection, it is worthy of note that persons tested in this series showed normal steropsis [stereoscopic picture test] but did not exhibit the Pulfrich effect.)

(*b*) When perception of movement is impaired it is likely to involve perception of the Pulfrich effect.

(*c*) People do not see what they do not expect to see or are not used to seeing. Hence it is of prime importance to demonstrate the stereo-effect as impressively as possible to the patient before the quantitative testing starts, by creating a distinct brightness difference between the two eyes.

DEFINITION OF "NORMAL," "QUESTIONABLY ABNORMAL" AND "ABNORMAL" PULFRICH EFFECT

The Pulfrich effect was considered normal for differences of rotation up to 15 degrees from the normal observer, since difference of this magnitude occurred in the majority of patients. With differences over 15 and under 25 degrees the Pulfrich effect was called "questionably abnormal." The effect was considered "abnormal" when the patient required consistently in all 3 trials or in 3 out of 5 trials at least 25 degrees less rotation of the polaroid than does the normal observer.

RESULTS

Seventy-four male patients (white persons and Negroes) were examined in order to obtain some idea of the quantitative aspect of the Pulfrich effect; no attempt was made to select patients with such conditions as would most likely involve the visual sector. All patients were inmates of Eloise Hospital.

They presented the following diagnoses:

	No. of Patients
Alcoholism, chronic	4
Amyotrophic lateral sclerosis	1
Brain tumor (questionable)	2
Cerebellar ataxia	1
Convulsive disorder	3
Tumor of spinal cord	1
Senile dementia	1
Diabetes mellitus	1
Extirpation of right parieto-occipital subcortical area (gumma)	1
Dementia paralytica	3
Hemiplegia	5
Idiopathic epilepsy	1
Cerebral spastic infantile paralysis (Little's disease)	2
Cerebrospinal syphilis	5
Syphilis (peripheral neuritis)	1
Atrophy of optic nerve	1
Postencephalitic paralysis agitanis	3
Basophilic adenoma of the pituitary	1
Polycythemia vera	1
Cerebellopontile tumor	1
Multiple sclerosis	4
Tabes dorsalis	16
Tabetic form of dementia paralytica	2
Condition undiagnosed at the time of testing	13
Total	74

Testing these patients for the Pulfrich effect produced the following results:

1. Five patients demonstrated an abnormal Pulfrich effect. They presented the following diagnoses: tabes dorsalis, 2 patients; tabetic form of dementia paralytica, 1 patient; chronic alcoholism, 1 patient, and diabetes mellitus, 1 patient.

2. In 1 patient with tabes dorsalis there was a questionably abnormal Pulfrich effect.

3. In 1 patient with the diagnosis of "convulsive disorder" the Pulfrich effect became less distinct when the speed of the moving rod was decreased, in contrast to the normal situation, in which speed enhances perception of the stereoeffect.

4. In 2 patients the Pulfrich effect could be elicited for the one eye only. The condition of 1 of these patients was undiagnosed at the time of the testing. He was very intelligent; the pupils were of equal width, and stereopsis was present. The other patient offered a diagnostic problem, suggestive of cerebral tumor, syphilis of the central nervous system, chronic alcoholism or subdural hemorrhage. His vision was reduced, and the pupils were round, the left being smaller than the right. When the right eye was darkened, the Pulfrich effect was clearly experienced; but no degree of darkening of the left eye or any variation of speed was capable of eliciting the Pulfrich effect. This patient, too, had unimpaired stereopsis.

5. Seventeen patients did not experience the Pulfrich effect at all. For these patients the diagnoses were as follows: multiple sclerosis, 1; syphilis of the central nervous system, 2; postencephalitic paralysis agitans, 2; basophilic adenoma of the pituitary gland, 1; polycythemia vera, 1; dementia paralytica, 1 (this patient showed anisocoria, which, however, had failed to facilitate the Pulfrich effect); idiopathic epilepsy, 1 and senile dementia, 1. One patient was a girl of 13, with nausea, severe headache and oculomotor palsy. One patient was examined nineteen days after extirpation of a subcortical gumma in the right parieto-occiptal area; his stereopsis was unimpaired.

For 5 patients no diagnosis had been made at the time of the testing. Three of them appeared to have normal stereopsis, but in the fourth the existence of stereopsis remained in doubt.

6. Twelve patients were so inconsistent or noncooperative that no evaluation of their results was possible.

7. The remainder, of 36 patients, matched the Pulfrich threshold of the normal observer.

COMMENT

Site of the Normal Pulfrich Effect.—The most likely site of the Pulfrich effect is a synaptic delay in conduction of the optic impulse at the level of the retinal ganglion cells.

Origin of the Abnormal Pulfrich Effect.—The abnormal Pulfrich effect may indicate an intensified synaptic delay. It is premature to theorize on the causes of such delay, i. e., whether the electrical or the chemical factors involved in the transmission of impulses have undergone changes. Clinically it has been known for decades that in cases of tabes the perception of pain resulting from peripheral stimulation may be considerably delayed.

Another possible cause of the abnormal Pulfrich effect is demyelination of the nerve fiber itself, with consecutive slowing of conduction.

A study of the correlation between the abnormal Pulfrich effect and neurohistopathologic changes is highly desirable but may encounter difficulties. The "sensitivity" of the Pulfrich effect is high—it is possible to register differences of less than 0.001 second between visual sensation on the right side and that on the left—and this indication of deteriorating function may well precede the histochemically demonstrable changes of structure.

Another field of study is the correlation of the Pulfrich effect, stereopsis and perception of movement. The setup for eliciting the Pulfrich effect is flexible, lending itself to many modifications and being capable of both a high degree of accuracy and technical simplicity for clinical studies.

The influences of dark adaptation and pupillary dilation on the quantitative outcome of the rotation of the light-reducing polaroid remain to be studied.

Dark adaptation of the darkened eye would increase the apparent brightness, while the pupillary dilation would tend to counteract the reduction of intensity of the incident light. It is unknown to what extent the speed of transmission of impulses depends on (1) the physical intensity of the light stimulus and (2) the state of adaptation, i. e., the intensity of the sensation. It appears, however, from the uniformity of values for the same observer, as well as from the agreement among many other observers, that any modification introduced by adaptation and pupillary reflex is accounted for by an allowance of up to 15 degrees of rotation. When the outer polaroid is rotated rapidly and the judgment is made accordingly, the influence of adaptation is made negligible. As to the pupillary reaction, it may prove advantageous to employ an artificial pupil in front of each eye.

Analysis of Cases.—Only a superficial analysis of the results for the relatively small number of patients is possible.

The largest number of subjects with an abnormal or a questionably abnormal Pulfrich effect is found among tabetic patients. All these patients exhibited the Argyll Robertson phenomenon; in 3 of them the pupils were of equal size, while in a fourth the right pupil was barely appreciably smaller than the left. The 2 other, nontabetic, patients reacted normally to light. This predominance of tabetic patients may be significant; however, it must be remembered that the number of patients with the diagnosis of tabes dorsalis and the tabetic form of dementia paralytica by far exceeds that of the patients with any other disease examined.

One of the patients with a convulsive disorder had undoubtedly some visual disturbance. He recognized the rod when in movement or in the resting position but complained of haziness of the outlines. Whereas normally the Pulfrich effect is enhanced by increasing the speed of the moving rod, the opposite phenomenon—enhancement by decreasing the speed—was observed in this patient. This paradoxic reaction could be explained on the basis of impaired perception of movement, which increases with increasing speed. Within a limited range, perception of the moving rod was adequate to assure the Pulfrich effect.

An explanation of the seemingly queer phenomenon in the 2 patients exhibiting the effect in one eye only cannot be offered. The presence of the Pulfrich effect when the one eye was darkened and its absence when the other eye was darkened would theoretically mean that, although stereovision exists when, say, the right eye receives less light than the left eye, the patient cannot maintain stereovision if the other (left) eye receives less light. I know of no experiments in which static stereopsis has been studied under conditions of brightness differences for the right and for the left eye.

CONCLUSIONS

The assumption has been confirmed that unilateral delay of perception of visual impulses can be demonstrated with simple means which transpose the time difference into a spatial pattern.

The presence of such unilateral delay may be the first sign of a lesion in one optic nerve.

The simplicity and sensitivity of the described method promise to facilitate the discovery of pathologic changes at an early state.

In the diagram, *SS* indicates the plane of the illuminated background (screen); *n*, the position of the fixed metal rod, extending from the upper frame, and $m \rightarrow {}^{m}{}_{m} \leftarrow m$, the moving rod entering the visual field from the left, coinciding with the position of the fixed rod midway and returning from the right. The left (A_1) and the right (A_2) eye look at the fixed rod *n*, as designated by the lines of vision $A_1\ n$ and $A_2\ n$. A darkening device is indicated in front of the left eye A_1.

When the moving rod on its way from the left to the right is localized at m'_2 by the right eye, A_2, the delayed perception of the left eye results in a lag, so that the moving rod is localized for the "slower" eye at m'_1; this double localization, however, produces not two images, but one image, localized at the intersection of $A_1\ m'_1$ and $A_2\ m'_2$, in m', behind the plane of actual movement. At the two points of reversal of movement, when the rod comes to a standstill, the two eyes localize the rod at the same place. When the rod returns from the right point of reversal, the right eye sees the rod at m_2'', while the left eye localizes

GRAPHIC DESCRIPTION OF THE PULFRICH EFFECT (FIGURE)

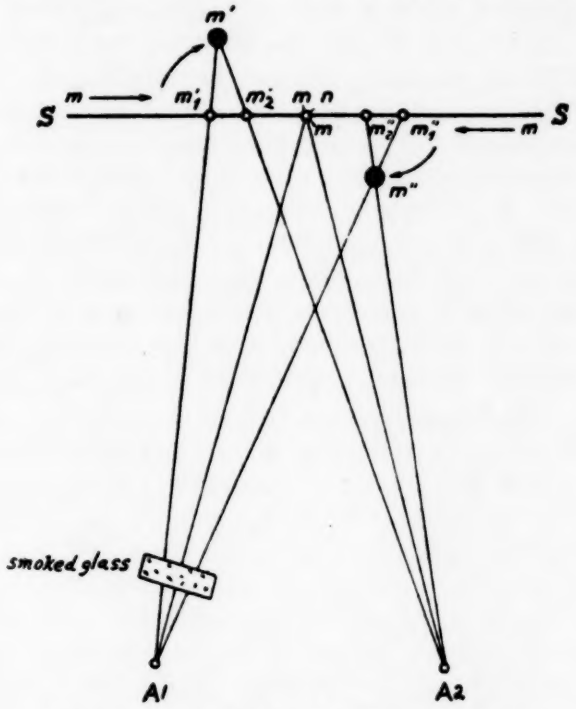

Diagram of the Pulfrich effect (after Pulfrich [2]).

the rod at m_1''; binocular localization occurs at m'', in front of the plane SS, at the point of intersection of $A_1\ m_1''$ and $A_2\ m_2''$. Thus, a clockwise movement results from delaying the perception of the left eye, and a counterclock movement, from delaying perception of the right eye.

SUMMARY

When a normal observer looks at a pendulum swinging in front of an illuminated background and a smoked glass is placed in front of one eye, the pendulum appears suddenly to describe a horizontal circle. This stereoeffect—the so-called Pulfrich effect—results from

a lag of perception originating in the eye behind the smoked glass. The physiologic basis of the Pulfrich effect is probably the slower conduction of impulses and/or transmission of the weaker of two, otherwise identical, stimuli.

This normal Pulfrich effect is elicited by a brightness difference of certain magnitude between the illuminations of the two eyes. It is assumed that in persons with a pathologic condition of one optic nerve abnormal delay in conduction and/or transmission of impulses may be an early occurrence. This delay, however, at its early stage, may be below the threshold of perceptibility, requiring a special "magnifying" device for demonstration.

The assumption is made that for persons with such subthreshold delay the light intensity for the eye on the affected side requires less reduction than for a normal observer in order to make the Pulfrich effect manifest.

A simple method of producing and measuring the Pulfrich effect by means of a moving rod and two pairs of polaroids is described.

Examination of 74 patients selected at random revealed the actual existence of abnormal unilateral delays in 5, possibly 6, patients.

Relations of the Pulfrich effect, static stereopsis and perception of movement and the site and cause of the abnormal Pulfrich effect are discussed, and the study of correlations between the abnormal effect and histopathologic changes is suggested.

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DOMINANT BRAIN WAVE FREQUENCIES AS MEASURES OF PHYSICOCHEMICAL PROCESSES IN CEREBRAL CORTEX

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IT IS now well known that the electroencephalogram is modified by a variety of factors influencing the physicochemical environment of the brain. Studies of the effects of such agents as carbon dioxide, oxygen tension, blood sugar, temperature and drugs have been made by many investigators on the measurable variables: per cent time present of the alpha activity, delta index, dominant frequency (usually the alpha frequency), wave amplitude or voltage and the form of the frequency spectrum. In this paper we point out why we believe that one of these measures is superior to the others for furnishing information about the chemical dynamics of the cortex and show why some current methods of analysis of frequencies in the electroencephalogram, while empirically interesting, must give discrepant results when compared with other methods.

The most conspicuous aspect of the normal electroencephalogram is usually the alpha rhythm. This is a rhythm of a specific frequency, characteristic of the individual subject, of from 8 to 13 cycles per second. The waves are easily recognized in most records and are of sinusoidal form. The constancy of their frequency for a given person suggests their production by basic, constant chemical dynamics. The alpha frequency per se is little affected by sensory stimuli, and in this way it is in sharp contrast to measures of the amount of time the alpha waves are present in the record, i.e., to the "per cent time alpha activity." For example, when the eyes are open, the alpha frequency is the same as, or perhaps ½ cycle faster than, it is when they are closed; but the per cent of time the alpha activity is present is greatly decreased, or the rhythm may even be eliminated for a time, when the eyes are open.

In like manner, it is a commonplace experience of students of the electroencephalogram to find in a given group of relaxed subjects with closed eyes, all of whom show a clearly countable alpha frequency of, say, 10 cycles per second, that these waves may vary from 10 to 90 per

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cent in the percentage of time they are present. Thus, the frequency of the alpha rhythm and the per cent of time it is present are independently variable and must therefore be controlled by quite different mechanisms. Any method of analysis that fails to recognize this and measures these two variables indiscriminately is not in a position to delineate underlying determinants of either one, despite the empiric changes it may reveal in gross properties of the brain waves when the chemical environment of the brain is modified by physiologic agents.

It is generally accepted that the amplitude of the waves is a rough measure of the number of cellular units contributing to the voltage. The frequency of the waves has been shown to be determined by quite different factors, which we shall discuss. Little is known about the mechanism underlying the percentage of time the alpha waves are present beyond the unproved hypothesis that it depends on the synchrony of the units contributing to the response, which is destroyed by afferent stimulation. Why some people have much and others little or no alpha activity is unknown.

Frequency in terms of waves per second is by definition a rate; and one is tempted to ask, a rate of what? In a series of papers, beginning in 1936, one of us (H. H.) and collaborators investigated this problem by studying the relation of the dominant, or alpha, frequency to aspects of cerebral metabolism. It was shown that the alpha frequency in man, when studied in relation to the internal body temperature (by means of diathermy) follows the Arrhenius equation known to describe the velocity of chemical reactions as a function of temperature. Of much more significance was the observation that the activation energy, or temperature characteristic, of the alpha rhythm calculated from this equation gave three values, each one of which has frequently been encountered in measurements of oxidation rates of cell suspensions and tissue slices in vitro.[1] We have been able to identify two of these values with specific enzyme systems extracted from tissues.[2] One corresponds to the activation energy of the oxygen-activating cytochrome system prominent in most tissues, including brain, and the other, to the no less important dehydrogenase enzyme that converts succinate to fumarate, thereby furnishing hydrogen to combine with

1. Hoagland, H.: Pacemakers of Human Brain Waves in Normals and in General Paretics, Am. J. Physiol. **116**:604-515, 1936; Some Pacemaker Aspects of Rhythmic Activity in the Nervous System, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, N. Y., The Biological Laboratory, 1936, vol. 4, pp. 267-284.

2. Hadidian, Z., and Hoagland, H.: Chemical Pacemakers: I. Catalytic Brain Iron; II. Activation Energies of Chemical Pacemakers, J. Gen. Physiol. **23**:81-99, 1939; III. Activation Energies of Some Rate-Limiting Components of Respiratory Systems, ibid. **24**:339-352, 1941.

the cytochrome-activated oxygen. The third value of activation energy for alpha brain wave frequencies has not as yet been related to any specific enzyme system. This last value characterizes the normal electroencephalogram. The values corresponding to succinodehydrogenase and to the cytochrome system were encountered at various advancing stages of dementia paralytica. These results could be accounted for satisfactorily by the view that the frequency of the alpha rhythm is directly proportional to the velocity of a chemical pacemaker or bottleneck in the serial chain of enzyme-catalyzed events involved in cerebral respiration. Syphilitic encephalitis apparently alters the relative velocities of various steps in cerebral respiration, so that with the progression of the disease the slowest step in the respiratory chain shifts, with the result that first one, and later another, step becomes the chemical pacemaker. Our studies of the relation of alpha frequencies to the sugar [3] and oxygen[4] of the blood, to dinitrophenol [5] and to thyroxin [6] all were consistent with these general observations.

It should be made clear, however, that it is the change in the alpha frequency that is proportional to the change in the cellular respiration. The absolute rate, e. g., 10 cycles per second, is contingent on the electrical constants of the tissues as well as on the respiratory rate of the cells, and these constants are only indirectly related to oxidative events. A recent review of the work on chemical pacemakers in relation to the frequencies of physiologic events has been made by Hoagland.[7]

In the studies previously mentioned, frequencies were obtained by simply counting the number of alpha waves per second in the records with dominant alpha activity for large samples and averaging, so that mean values statistically significant to 0.1 cycle per second were obtained.

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3. Hoagland, H.; Rubin, M. A., and Cameron, D. E.: Electroencephalogram of Schizophrenics During Insulin Hypoglycemia and Recovery, Am. J. Physiol. **120**:559-570, 1937.

4. Himwich, H. E.; Hadidian, Z.; Fazekas, J. F., and Hoagland, H.: Cerebral Metabolism and Electrical Activity During Insulin Hypoglycemia in Man, Am. J. Physiol. **125**:578-585, 1939.

5. Hoagland, H.; Rubin, M. A., and Cameron, D. E.: Brain Wave Frequencies and Cellular Metabolism: Effects of Dinitrophenol, J. Neurophysiol. **2**:170-172, 1939.

6. Rubin, M. A.; Cohen, L. H., and Hoagland, H.: The Effect of Artificially Raised Metabolic Rate on Electroencephalogram of Schizophrenic Patients, Endocrinology **21**:536-540, 1937.

7. Hoagland, H.: Chemical Pacemakers and Physiological Rhythms, in Alexander, J.: Colloid Chemistry, New York, Reinhold Publishing Corporation, 1944, vol. 5, pp. 762-785.

Recently, Engel and collaborators [8] have used a new method of frequency analysis in studies of effects of physiologic agents on the electroencephalogram. This method is different from that which we have used for defining and measuring the dominant frequency, and quantitative agreement between the methods could not be expected. Brazier, Finesinger and Schwab,[9] on the other hand, have developed what seems to us a more satisfactory method of dealing with the electroencephalographic spectrum, based on studies of the dominant frequency or frequencies. Their method usually yields a main dominant frequency identical with the alpha rhythm as we have studied it. Since we have found that quantitative changes in such frequencies may serve as a direct key to underlying chemical kinetics, we wish to compare these methods and to show that the frequency analysis of Engel and associates, while empirically interesting and superficially similar to that of Brazier and Finesinger, actually measures a combination of two independent variables and is not suitable on theoretic grounds for use in delineating controlling kinetic events as rates within the cells.

METHODS

Engel and associates described their method of analysis of the frequency spectrum of the electroencephalogram as follows:

> With the usual ruled paper (large divisions at one second intervals), the number of complete waves in each one second strip of record was counted. The count for the total of 300 one second intervals was made, and the distribution of frequencies per second was expressed as a percentage of the whole. . . . Stretches of low voltage fast activity, which were present in varying degrees in all records, were designated as such, and no attempt was made to estimate the individual waves, which were often not countable. When a given interval contained both countable waves and low voltage fast activity, the type which occupied

8. (*a*) Engel, G. L.; Romano, J.; Ferris, E. B.; Webb, J. P., and Stevens, C. D.: A Simple Method of Determining Frequency Spectrums in the Electroencephalogram, Arch. Neurol. & Psychiat. **51**:134-146 (Feb.) 1944. (*b*) Romano, J., and Engel, G. L.: Delirium: I. Electroencephalographic Data, ibid. **51**:356-377 (April) 1944. (*c*) Engel, G. L., and Romano, J.: Delirium: II. Reversibility of the Electroencephalogram with Experimental Procedures, ibid. **51**:378-392 (April) 1944. (*d*) Engel, G. L., and Rosenbaum, M.: Delirium: III. Electroencephalographic Changes Associated with Acute Alcoholic Intoxication, ibid. **53**:44-50 (Jan.) 1945.

9. (*a*) Brazier, M. A. B., and Finesinger, J. E.: Characteristics of the Normal Electroencephalogram: I. A Study of the Occipital Cortical Potentials in 500 Normal Adults, J. Clin. Investigation **23**:303-311, 1944. (*b*) Brazier, M. A. B.; Finesinger, J. E., and Schwab, R. S.: Characteristics of the Normal Electroencephalogram: II. The Effect of Varying Blood Sugar Levels on the Occipital Cortical Potentials in Adults During Quiet Breathing, ibid. **23**:313-317, 1944; (*c*) III. The Effect of Varying Blood Sugar Levels on the Occipital Cortical Potentials in Adults During Hyperventilation, ibid. **23**:319-323, 1944.

the greater portion of that interval was arbitrarily selected for purposes of designation.

Such an ana'ysis yields a "spectrum" of frequencies ranging from 1 to 12 per second, together with some low voltage activity. It should be emphasized, however, that this is not a true spectrum of frequencies in that the percentages of one second intervals containing 8 waves, 9 waves, 10 waves, etc., rather than the percentages of 8 per second waves, 9 per second waves, 10 per second waves, etc., are given. In other words, the distribution of waves per second, rather than the distribution of individual wavelengths, is determined. The latter is a tedious process and involves measurement of the length of each wave with a caliper of some sort. Our method may give a slightly false impression of the distribution of wavelengths greater and less than the dominant one, for waves of these frequencies will tend to be averaged with waves of the dominant frequency and hence may appear in somewhat lower proportion than is actually the case. For example, if 2 or 3 waves of 5 per second frequency should appear with 8 per second waves in a one second interval, the number of waves in that interval would be recorded as 6 or 7, and the figure would not reveal the presence of 5 per second waves. This will not obscure any shift toward faster or slower frequencies, and no error in interpretation will result if it is remembered that the method gives the distribution of average frequencies per second rather than the distribution of wavelengths . . .

Brazier and Finesinger [9a] described their method as follows:

In order to compile a frequency distribution curve, a 2-minute record . . . is first inspected for the presence of artefacts. Any portion showing artefacts due to eye-blinks, muscle movements, etc., is omitted from the sample for analysis. The remainder is measured for total length of time, and this figure becomes the total on which all percentages are calculated.

A transparent grating, marked off in intervals equivalent to each of the frequencies, is then laid on the record, and the frequency of any chains of waves is thus easily determined. The time covered by waves of each frequency is then totaled, the results being expressed as percentages of the whole period measured.

RESULTS

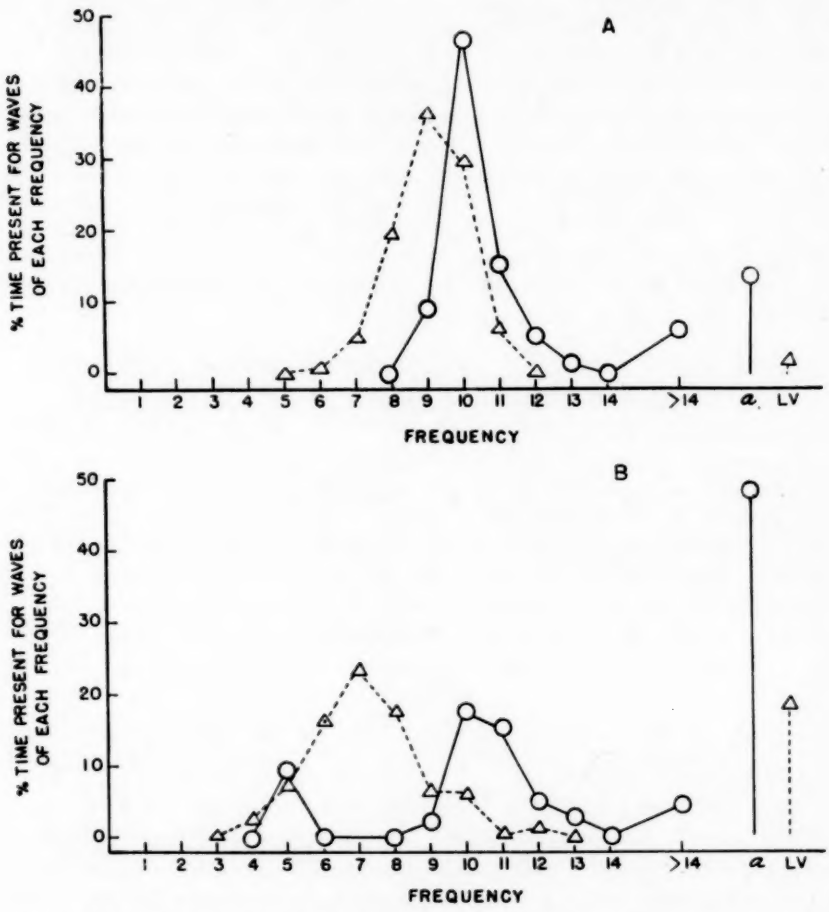
Results of both these methods can best be expressed graphically as plots, in which frequency of waves, as the abscissa, is plotted against the percentage of time the particular frequency is present, as the ordinate. Both show a dominant frequency, but the two methods measure quite different things, owing to the different definitions of frequency involved. Brazier's method yields a dominant frequency that corresponds to a true rate; Engel's method yields a measure that is a composite of frequency and per cent of time the frequency is present. Since it thus lumps into one numerical unit at least two quite independent processes, it cannot serve as an index of rates of change of underlying chemical mechanisms.

This may best be illustrated by applying the two methods to identical sections of the same record and comparing the results.

Electroencephalograms were taken on one of us (D. K.) for five minutes with the subject's eyes closed and immediately afterward for

five minutes with his eyes open. Standard recordings were made from bipolar leads from the right and the left occiput. The same parts of the records were analyzed by the Engel method and by the Brazier method, and the chart shows the results.

With the eyes closed the Brazier method shows a dominant alpha frequency of 10 cycles per second, and this frequency, qua frequency, is not significantly changed by opening the eyes; but it drops from 46.5



A, analysis of five minutes of a recording taken when the eyes were closed, with the Brazier method (solid line and circles) and with the Engel method (dotted line and triangles). *B*, similar analysis of another five minute recording taken immediately after *A* was obtained, with the eyes open.

α refers to arhythmic waves (Brazier method), and *LV*, to low voltage fast waves (Engel method). For discussion, see text.

to 14.2 per cent of time present when the eyes are opened. In this record a 5 cycles per second rhythm also appears when the eyes are open. The dominant frequency as analyzed by the Engel method is 9

cycles per second with the eyes closed and as 7 cycles per second when they are opened.

Since opening the eyes greatly decreases the per cent of time the alpha activity is present without altering the frequency, and since the Engel method counts as frequency the total number of heterogeneous waves within a second interval, a decrease in the per cent of time the dominant frequency is present would inevitably give fewer waves per second with the Engel method, resulting in an apparent lowering of the dominant frequency. The Engel method introduces into the measurement of frequency the process concerned with determining the per cent of time the frequency is present, and since the mechanism underlying this is clearly independent of the mechanism determining

Dominant Frequencies in Electroencephalograms of Four Subjects Taken on Five Different Occasions

Subject	Date (1945)	Dominant Frequency, Engel Method (±0.5 Cycle)	Dominant Frequency, Brazier Method (±0.5 Cycle)	% Time Present of Dominant Frequency, Brazier Method
J. D.	4/12	8	10	40
	4/14	8	10	38
	4/18	8	10	42
	4/19	8	10	41
	4/21	7	10	35
I. C. K.	4/11	10	10	63
	4/16	10	10	71
	4/17	9	10	56
	4/18	10	10	72
	4/19	9	10	58
I. M.	4/16	8	10	40
	4/19	7	10	18
	4/21	8	10	52
	4/23	7	10	29
	4/25	9	10	64
A. T.	4/18	8	11	49
	4/19	8	11	48
	4/21	8	11	52
	4/23	8	11	56
	4/24	7	11	35

the frequency itself, it is apparent that the two methods are not concerned with the same basic phenomenon.

The table shows dominant frequencies of the electroencephalograms taken on five occasions from each of 4 subjects. The dominant alpha rhythm is constant for each subject, but analysis by the Engel method shows day to day variation in their dominant frequency. This variation is due to variation in the percentage of time the alpha rhythm is present, as may be seen from the table. Low per cent time alpha gives a low value for the dominant frequency; high per cent time alpha yields a higher dominant frequency.

COMMENT

Engel and associates [8a] (page 135) note that their method "may give a slightly false impression of the distribution of wavelengths greater and less than the dominant one" since they do not measure

wavelength but take as the frequency the total number of waves per second. Our main criticism is that the method is misleading in its misuse of the concept of the dominant frequency itself if one considers waves of similar length arranged in sequences as reflecting physicochemical processes in the cells. Engel and his collaborators are concerned with the effects of physiologic agents on the electroencephalogram, and, while empiric changes are of course brought out by their method, it seems unfortunate to employ a tool which by its very nature, through its definition of "frequency," masks the possibility of a rational interpretation of rates of events going on in the brain.

The dominant frequency as studied with the Brazier method is the frequency which we have used in our earlier studies of the effects of physicochemical agents on the electroencephalogram. It would, for example, be quite impossible on theoretic grounds to calculate meaningful energies of activation of enzyme steps in the carbohydrate cycle with the method of Engel and associates, since their frequencies, including their dominant frequencies, are composed of waves of different lengths and the independent variable, the per cent time alpha, contributes to the determination of their actual frequencies per se.

This may be illustrated by a hypothetic example. Suppose one has a record composed of continuous and uniform sine waves of 10 per second produced by a piece of electrical apparatus. There would thus be only one frequency, the dominant one determined by the properties of the apparatus making the signals. One may now consider an equal length of record consisting of five second strips of the same 10 per second waves, alternating with equal intervals with no waves at all. Such a record could be made artificially by turning the apparatus that makes the waves on and off at five second intervals. The dominant rhythm in both these records, according to our studies and to the Brazier method, is clearly 10 cycles per second; the dominant rhythm according to the Engel method is 10 per second in the first record and 5 per second in the second record, and from this one would be led to the erroneous conclusion that the apparatus producing the waves with a frequency of 5 per second was operating at half its former rate.

For the reasons we have discussed, the measurements of Engel and associates cannot reflect the rates of changes of kinetic processes in the brain, and in effect they mask these processes. The Engel spectrum is a graphic representation of gross qualitative changes observed in the records, and as an analytic instrument it has all the limitations of the delta index,[3] which we have described and have used as a purely empiric expression of the numerical representation of the magnitude of slow wave activity in the electroencephalogram. Quantitative changes with physiologic variables of bands of waves of equal length (e. g., the

alpha waves) have led to significant insight into the chemical kinetics of the brain, and further studies along these lines hold promise. Much of the value of this type of investigation may be lost unless the limitations of the methods used are borne in mind.

SUMMARY

Use of the dominant alpha frequency as a measure of chemical kinetics of cerebral processes is discussed.

Advantages of the method of Brazier and Finesinger for plotting electroencephalographic frequency spectrums are considered and compared with those of the method of Engel and associates.

It is concluded that the Engel method does not furnish a concept of frequency that lends itself to analysis of the chemical kinetics of cerebral processes.

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IS RESTORATION OF INHIBITED CONDITIONED REACTIONS BY INSULIN COMA SPECIFIC FOR PAVLOVIAN INHIBITIONS?

Contribution to the Theory of Shock Treatment

ERNST GELLHORN, M.D.
MINNEAPOLIS

IN a series of papers by Gellhorn and collaborators [1] it was shown that insulin hypoglycemia, especially in the form of insulin coma, and chemically or electrically induced convulsions lead to a restoration of inhibited conditioned reactions. In this work, conditioning of the escape reaction resulting from subjection of the experimental animal (rat) to a slight electric shock was accomplished by the simultaneous presentation of various sensory stimuli. After the conditioned reaction had been fully established, it was gradually inhibited by lack of reenforcement (Pavlov's internal inhibition). Spontaneous recovery of such inhibited reactions did not occur, but a restoration could be induced with great regularity if the animals were subjected to insulin coma and related forms of "shock treatment."

Furthermore, it was observed [2] that if two or more conditioned reactions were studied in the same animal insulin coma and related forms of "shock treatment" acted only on the inhibited conditioned reactions but did not alter the positively established conditioned reactions. However, before a generalization of this statement was suggested, it seemed desirable to investigate a positively established conditioned reaction which in outward appearance was similar to the inhibited conditioned reaction used previously. If it were possible to show that a

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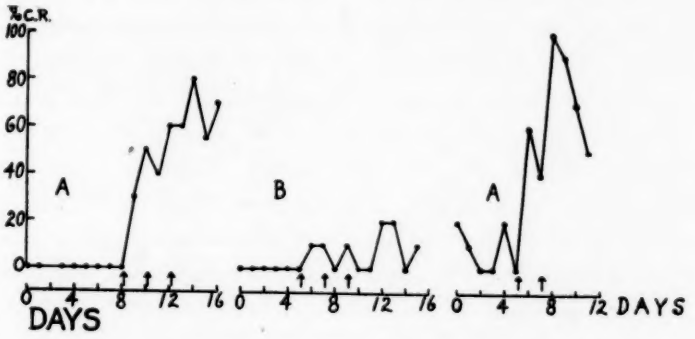
From the Division of Neurophysiology, Department of Physiology, University of Minnesota Medical School.

1. (*a*) Gellhorn, E.; Kessler, M., and Minatoya, H.: Influence of Metrazol, Insulin Hypoglycemia and Electrically Induced Convulsions on Reestablishment of Inhibited Conditioned Reflexes, Proc. Soc. Exper. Biol. & Med. **50**:260-262, 1942. (*b*) Gellhorn, E., and Minatoya, H.: The Effect of Insulin Hypoglycemia on Conditioned Reflexes, J. Neurophysiol. **6**:161-171, 1943. (*c*) Kessler, M., and Gellhorn, E.: The Effect of Electrically and Chemically Induced Convulsions on Conditioned Reflexes, Am. J. Psychiat. **99**:687-691, 1943. (*d*) Gellhorn, E.: Studies on Conditioned Reactions and Their Clinical Implications, Journal-Lancet **63**:307-312, 1943.

2. Gellhorn, E.: Further Investigations on the Recovery of Inhibited Conditioned Reactions, Proc. Soc. Exper. Biol. & Med. **59**:155-161, 1945.

positively established conditioned reaction resulting in suppression of a motor action would react differently to insulin coma than a negatively established conditioned reaction in which the animal likewise refrained from motor activity because the latter had been inhibited by lack of reenforcement, a new light would be thrown on the physiologic nature of the insulin effect.

The main group of experiments, following a series of preliminary observations, was performed on 11 rats. In contrast to the apparatus used in the earlier work, which consisted of two chambers only, a circular apparatus divided into six chambers, was employed, which permitted the rats to escape from the shock into either of the two adjacent divisions. After the conditioned reaction was established, it was inhibited by lack of reenforcement, as in my earlier work. Then, insulin coma was applied, and the degree of recovery of the conditioned reaction was ascertained. This constituted the first part of the experiment (A). Thereafter the conditioned reaction was again fully established by reenforcing the conditioned stimulus. Then, this conditioned reaction was abolished, not by



Effect of insulin coma on the recovery of the conditioned escape reaction after this reaction has been abolished by internal inhibition (*A*) or by application of a countershock (*B*). The ordinate represents the percentage of recovery of the conditioned reaction (*C. R.*); the abscissa, the time, in days. The arrows indicate injection of insulin, leading to coma.

internal inhibition but by countershock; i. e., the electrical shock was applied to the grid of the two adjacent chambers when the conditioned stimulus was presented. The rat jumped, of course, into one of the adjacent compartments and was driven back through the shock into the original compartment. Repetition of this procedure for several days abolished the conditioned reaction completely. Thereafter insulin coma was applied in the same manner as in the first part of the experiment, and the degree of recovery of the conditioned reaction was again determined. This section of the experiment is referred to as part B. Then the rat was again retrained; i. e., the conditioned reaction was again established by reenforcing the conditioned stimulus with the electric shock, and part A of the experiment was repeated.

RESULTS

A typical experiment is shown in the graph. The periods of training during which the conditioned stimulus (a muffled bell) was reenforced by a slight electrical shock applied to the grid of the com-

partment and the subsequent periods of inhibition by lack of reenforcement are omitted in the presentation of part A of the experiment. Likewise, the establishment of the conditioned reaction and its abolishment by countershock are not recorded in part B of the graph. The record shows that when the conditioned reaction had been abolished by lack of reenforcement (A) the administration of insulin leading to coma induced the recovery of the conditioned reaction. If, however, the conditioned reaction had been eliminated by countershock, no significant recovery [3] of the conditioned reaction occurred. It is noteworthy that when part A was repeated in the experiment recorded in the graph two insulin comas were sufficient to cause a temporary recovery of the conditioned reaction of 100 per cent, so that the third coma could be omitted. The failure of insulin coma to produce recovery of the previously established positive conditioned reaction after countershock had been applied was obviously not due to a spontaneous change in

Percentages of Recovery of Conditioned Reactions with Insulin Coma

No.	Percentages of Recovery		
	A*	B*	A*
30	50	10	30
37	50	30	50
7	50	20	50
55	50	10	..
29	90	10	..
52	50	20	..
60	..	20	70
64	50	10	..
36	50	20	50
31	80	20	..

* In column A fall the conditioned reactions inhibited by lack of reenforcement; in column B, those abolished by countershock.

the animal, since a repetition of part A after part B had been completed showed again the striking effects of recovery of an inhibited conditioned reaction induced with insulin coma. This result was confirmed in 10 more experiments, listed in the accompanying table in which it is also shown that the sequence of the two parts of the experiments (A and B, or B and A) is immaterial to the results. The recovery of the abolished conditioned reaction through insulin coma is possible only when this reaction has been eliminated by internal inhibition, and not when countershock is the cause of a new learning process leading to a new attitude (avoidance reaction) of the animal.

The clue to an understanding of the experiments just described seems to lie in the fact that the significance of the conditioned stimulus (bell), previously the signal for an escape reaction, was altered by its combination with the countershock. In these circumstances the escape

3. An increase of about 20 per cent was found to be insignificant in the experiments of Gellhorn and Minatoya.[1b]

reaction was suppressed and the behavior of the animals was overtly similar to that seen after internal inhibition. But important physiologic differences existed between these two situations. In the conditions present in part A of the experiment the temporary association between the conditioned reaction and the conditioned stimulus still existed, although in an ineffectual form, so that, owing to the lowered excitability of the brain as a whole as a result of internal inhibition,[4] the conditioned stimulus was unable to elicit the positive escape reaction (conditioned reaction). Under the influence of repeated insulin coma or similar procedures (electric shock and metrazol convulsions) these weak links between the conditioned stimulus and the unconditioned reactions are apparently intensified, and thus the original escape reaction reappears in response to the conditioned stimulus (bell). In the case, however, in which the conditioned reaction was abolished by countershock the situation is quite different, since a new positive conditioned reaction is substituted for the old one. The bell was the signal for an escape reaction during part A and the early portion of part B; but, whereas it retained this physiologic and symbolic significance in part A, although it lost its effectiveness, owing to lack of reenforcement, the bell became the signal for a new avoidance reaction in the crucial portion of part B. Since this reaction was established under the influence of a strong unconditioned stimulus (countershock), it replaced quickly the former conditioned reaction. The new behavior was easily acquired and apparently elicited a very stable conditioned reaction, in which the animal, on exposure to sound, refrained from escaping into the adjacent compartments. If the action of insulin coma and related procedures would produce an increase in the general level of excitability, it might cause an animal to react to the bell with a vigorous escape reaction in the two situations represented by parts A and B of the experiment, regardless of the fundamental difference in the nature of the physiologic reactions which form the basis of the behavior of the animal in the two parts of the experiment. The experimental results show clearly that this is not the case. The specificity with which insulin coma (and probably electrically induced convulsions) restores inhibited conditioned reactions without affecting the avoidance reaction established by countershock indicates clearly that these procedures act only on those cortical processes which, although latent during internal inhibition, are the basis of the conditioned reaction. This interpretation is in agreement with the observations in previous studies in which the effectiveness of insulin coma and electric shock in the restoration of inhibited conditioned reactions was directly related to

4. The reader is reminded of Pavlov's demonstration of the relation of internal inhibition to sleep.

the stability of the conditioned reaction. Reactions to a bell, which were established with ease but abolished with difficulty, were more effectively restored with insulin coma or electric shock than were conditioned reactions to a light, which showed the opposite behavior, indicating a lesser degree of stability. On the other hand, the results of experiments reported in this, as well as in the preceding, paper seem to warrant the statement that positive conditioned reactions, no matter whether the conditioned reaction consists in a movement or in the suppression of a movement, are not altered by insulin coma.

Numerous studies have shown that the centers of the sympathetic system become more excitable as a result of insulin coma, electric shock and similar procedures.[5] Such effects may persist for considerable periods.[6] It must therefore be assumed that discharges from these centers, particularly from the hypothalamus, are increased above the normal value. Murphy and Gellhorn [7] showed recently that the sympathetic parts of the hypothalamus give rise to impulses afferent to the motor cortex, the primary sensory projection area and the association centers of the brain. These impulses increase the effectiveness of subthreshold stimulation of the motor cortex to such a degree that distinct movements may result. Furthermore, studies of the action potentials of the cortex have shown that under the influence of these hypothalamic impulses the cortical excitability is greatly increased and the number of active neurons enlarged.[7] These data suggest that cortical residues of previously established conditioned reactions may be activated as a result of the heightened hypothalamic activity following insulin coma. This may account for the restoration of inhibited conditioned reactions. That no generalized, nonspecific excitatory effects follow insulin coma is indicated by the fact that insulin coma becomes ineffective after suppression of the original conditioned reaction by the establishment of a new one (avoidance reaction).

To what extent these data are helpful in the interpretation of the mental changes characterizing psychoses for which "shock therapy" has been found to be of value, as well as in the understanding of the mechanism of recovery as the result of this form of therapy, remains to be determined by clinical investigators. However, the frequently recurrent statement in the clinical literature that nothing is known

5. Gellhorn, E.: Autonomic Regulations, New York, Interscience Publishers, Inc., 1943.

6. Gellhorn, E.: The Role of the Autonomic Nervous System in Problems of Rehabilitation, Federation Proc. **3**:266-271, 1944.

7. Murphy, J. P., and Gellhorn, E.: Hypothalamic Facilitation of the Motor Cortex, Proc. Soc. Exper. Biol. & Med. **58**:114-116, 1945; The Influence of Hypothalamic Stimulation on Cortically Induced Movements and on Action Potentials of the Cortex, J. Neurophysiol. **8**:341-364, 1945.

of the mechanism of the shock treatment is no longer warranted by facts in view of the extensive physiologic work regarding the action of insulin coma and related conditions on the central nervous system.[8]

SUMMARY

A conditioned escape reaction inhibited through lack of reenforcement is restored by insulin coma and related procedures, as shown in previous studies. If, however, the escape reaction is abolished by countershock, i. e., by a shock applied to the adjacent compartments into which the rat escapes, treatment with insulin coma does not restore the escape reaction.

Although outwardly similar, the absence of the escape reaction in the two situations is based on dissimilar mechanisms. In the first situation a conditioned reaction disappears through lack of reenforcement, whereas in the second a new conditioned reaction is established by countershock. In agreement with a previous study, it is found that insulin coma acts only on inhibited conditioned reactions but does not influence positive conditioned reactions. The statement applies to the excitatory, as well as to the "inhibitory," type of the conditioned reaction.

It is suggested that the recovery of inhibited conditioned reactions with insulin coma is due to increased hypothalamic discharges to the cortex, which, according to investigations of Murphy and Gellhorn, may make subthreshold cortical processes supraliminal.

Miss Janet Bechtel assisted in this study.

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8. Gellhorn,[5] chap. 19. The Autonomic Nervous System and Neuropsychiatry: Effects of Hypoglycemia and Anoxia and the Central Nervous System, Arch. Neurol. & Psychiat. **40**:125-146 (July) 1938.

News and Comment

NEUROPSYCHIATRIC INSTITUTE AT THE MEDICAL COLLEGE OF ALABAMA

A neuropsychiatric institute has been created at the Medical College of Alabama and will be located in the school's teaching hospital, the Jefferson and Hillman hospitals, which will house on one floor the newly formed department of neurosurgery, neurology and psychiatry and all patients of the institute. Diagnostic, therapeutic, research and teaching services of the institute will be available to members of the medical profession at large.

This neuropsychiatric institute has been made possible by the Walter Haynes Foundation, which will subsidize study and research, in addition to the activities of the institute.

The staff of the institute is the same as that of the newly created department of neurology, neurosurgery and psychiatry: Walter G. Haynes, M.D., professor and chairman (neurosurgery), director of the Institute; Frank A. Kay, M.D., associate professor (psychiatry); Wilmot S. Littlejohn, M.D., associate professor (neurology); Donald Ramsdell, Ph.D., associate professor (psychology); Garber Galbraith, M.D., associate professor (neurosurgery); Samuel C. Little, M.D., assistant professor (neurology); William B. Patton, M.D., assistant professor (neurosurgery); Benjamin F. Morton, M.D., instructor (psychiatry); Stanley E. Graham, M.D., assistant, and William P. Tice, M.D., assistant.

CONTRACTS BETWEEN VETERANS ADMINISTRATION AND PRIVATE MENTAL HYGIENE CLINICS

Inquiries have been received in the Department of Medicine and Surgery as to whether the Veterans Administration will cancel contracts with private mental hygiene clinics for the outpatient treatment of veterans when the Veterans Administration Mental Hygiene Clinics are organized and functioning. This has resulted in hesitancy on the part of some clinics to negotiate contracts.

In respect to these inquiries, it is the policy of the Veterans Administration to continue all such contracts indefinitely, provided the caliber of work justifies their continuation.

AMERICAN PSYCHIATRIC ASSOCIATION

At the One Hundred and Second Annual Meeting of the American Psychiatric Association the following officers were elected: president, Dr. Samuel W. Hamilton, Washington, D. C.; president-elect, Dr. Winfred Overholser, Washington, D. C.; secretary-treasurer, Dr. Leo H. Bartemeier, General Motors Building, Detroit; Councillors: Dr. Kenneth Appel, Philadelphia; Dr. Karl M. Bowman, San Francisco; Dr. William C. Menninger, Topeka, Kan., and Dr. Thomas A. C. Rennie, New York.

SOUTHERN PSYCHIATRIC ASSOCIATION

The Southern Psychiatric Association will hold its annual convention in Richmond, Va., on Oct. 7 and 8, 1946. The list of speakers will be furnished within the next sixty days.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

ELECTROENCEPHALOGRAPHIC STUDIES DURING FEVER INDUCED BY TYPHOID VACCINE AND MALARIA IN PATIENTS WITH NEUROSYPHILIS. MILTON GREENBLATT and AUGUSTUS S. ROSE, Am. J. M. Sc. **207**:512 (April) 1944.

Greenblatt and Rose studied the brain wave patterns during the course of induced fever in 23 patients with neurosyphilis. Electroencephalographic tracings were obtained before the increase in temperature and at intervals of one-half to one hour during the fever. Observations on 54 paroxysms of fever were made, 34 of which were induced by injection of typhoid vaccine and 20 by malaria.

Before the fever the patterns of 8 of the patients were considered to be within normal limits, those of 5 were classed as borderline and those of 10 as abnormal. During the chill, the electroencephalogram showed evidence of pronounced muscular activity. The alterations in the tracing during the rise in temperature were: (1) an increase in the irregularity of the pattern, (2) an increase in the number of slow, or delta, waves and (3) an increase in the voltage of the potentials. The rise in temperature was associated with progressive loss of the characteristics of the patient's basic electroencephalogram, and the pattern at a high temperature (104 to 105 F.) was utterly different from that at the control temperature.

Several patients showed significant clinical changes during fever in the form of restlessness, irritability, listlessness and confusion. These patients showed the most striking changes in their electroencephalographic tracings. The main feature of the records was an increase in the slow, or delta, activity during fever.

It is believed that several influences, of which the metabolic rate is one, play a role in the alteration of the brain wave pattern during fever. The factors of temperature, metabolic rate, type of disease and type of induction of fever are considered as possible causal factors in the production of slow activity.

MICHAELS, M.C., A.U.S.

THE DISTRIBUTION OF DIPHOSPHOPYRIDINE NUCLEOTIDE IN THE BOVINE RETINA. C. B. ANFINSEN, J. Biol. Chem. **152**:279, 1944.

Quantitative histochemical studies of frozen-dried sections of the retina indicate that the concentration of diphosphopyridine nucleotide varies considerably from layer to layer in this organ. The highest concentrations were found in the two synaptic regions. The layer of ganglion cells also contained considerable quantities of the co-enzyme. The rods and the outer nuclear layer, however, contained much smaller amounts. The results have been discussed with regard to the possible role of diphosphopyridine nucleotide in the transmission of the visual impulse through the mediation of acetylcholine.

PAGE, Cleveland.

THE EFFECT OF GALVANIC EXERCISE ON DENERVATED AND RE-INNERVATED MUSCLES IN THE RABBIT. E. GUTMANN and L. GUTMANN, J. Neurol. & Psychiat. **7**:7 (Jan.-April) 1944.

In order to test the value of electrotherapy for peripheral nerve injury, the authors treated the muscles innervated by the peroneal nerve in a series of 30 rabbits. Galvanic current of about 4 to 6 milliamperes was used for about twenty minutes daily, and the results were compared with those for the untreated, opposite,

extremity. The experiments were divided into two groups: (1) treatment of denervated muscles without possibility of reinnervation and (2) treatment of muscles in which reinnervation was allowed. It was found that in both groups electrotherapy with a strength of current sufficient to elicit vigorous contractions of the muscles delayed or diminished muscular atrophy, as confirmed by biopsy. The most satisfactory results were obtained with a daily exercise of twenty to thirty minutes' duration. The effect was greater after short term (thirty-seven days) than after long term denervation (sixty-seven to one hundred and fifty days), and in the latter situation the earlier the treatment was started after denervation the greater the effect. Thus, after a maximal treatment beginning immediately after denervation the muscles lost only 17 per cent in weight in sixty days, as compared with a loss of 59 per cent in untreated muscles. The time of onset of motor recovery following various methods of reinnervation was not appreciably affected by the galvanic exercise, although the degree of motor recovery was higher in the treated muscles.

The results of these experiments showed that the effect of galvanic exercise varied with the time and duration of application of the current. No harmful effect of fatigue in denervated muscles was found. The effects of the treatment were still demonstrable four months after the galvanic exercise had been discontinued. Since there was no significant difference in intensity of fibrillations between treated and untreated muscles, the authors are of the opinion that atrophy and fibrillations are independent processes.

The observations suggest that activity is the leading factor in preventing muscular atrophy and that the impulses responsible for normal muscular activity which are lost after denervation can be effectively replaced by galvanic exercise. This is probably brought about by increased metabolism in the denervated muscles through a better circulation.

MALAMUD, San Francisco.

Psychiatry and Psychopathology

ELECTROENCEPHALOGRAPHY IN BEHAVIOR PROBLEM CHILDREN. CHARLES I. SOLOMON, WARREN T. BROWN and MAX DEUTSCHER, Am. J. Psychiat. **101**:51 (July) 1944.

Solomon, Brown and Deutscher studied the electroencephalograms of two groups of 20 boys each, one group comprising the best behaved and the other the worst behaved in a school class. The ages ranged from 13 to 16½ years. The authors chose this age range to avoid correlations between age differences and the electroencephalogram, concluding that at the age of 13 years normal adult patterns are developed. Social, economic and cultural backgrounds were similar for the two groups. The authors found 12 abnormal electroencephalograms among the 20 best behaved children and 11 among the worst behaved children.

The authors then studied in an institution for delinquent boys the electroencephalograms of the 10 least and the 10 most delinquent boys, finding abnormal patterns for 4 of the former and 9 of the latter. There was no correlation of the electroencephalographic pattern and intelligence, efficiency of performance or personality.

The highest incidence of abnormal electroencephalograms was found in the most poorly behaved institutional group, and this the authors conclude may indicate a physiologic disturbance influencing behavior. In view of the high incidence of abnormality found in normal children and the presence of normal and abnormal electroencephalograms among children presenting the same type of behavior problems, the authors conclude that it is difficult to interpret the significance of the electroencephalogram in an individual case. The presence of abnormalities can be considered only as an additional, unfavorable personal factor.

FORSTER, Philadelphia.

SPEECH IN SENILITY. FRED FELDMAN and D. EWEN CAMERON, Am. J. Psychiat. **101**:64 (July) 1944.

Feldman and Cameron studied the speech of psychotic senile patients and compared it grammatically with that of normal adults and children. The most prominent difference between senile and normal subjects was displayed in the use of pronouns, verbs and adjectives. Senile persons used pronouns and verbs more frequently and adjectives less frequently. The use of pronouns was attributed to the tendency of such persons to repetitiousness and hesitancy. The diminished use of adjectives by senile persons may indicate the failing capacity to express themselves by the more complex mechanisms of speech.

FORSTER, Philadelphia.

PERSONALITY CHANGES CHARACTERIZING THE TRANSITION FROM CIVILIAN TO MILITARY LIFE. GUSTAV BYCHOWSKI, J. Nerv. & Ment. Dis. **100**:289 (Sept.) 1944.

The transition from civilian to military life may, and often does, bring about personality changes in some persons. A number of mechanisms are responsible for the "preinduction anxiety" frequently seen. In some cases there is an abnormal fixation to the mother or to the wife, who represents a mother substitute. This is often rationalized as concern over her welfare. The fear of welfare of self is another frequent cause of preinduction anxiety. In men with a strong and insufficiently overcome castration complex this may take the form of fear of physical injury, while in others the threat of a potent and improperly integrated homosexual component may represent the real danger. A third important factor is the lack of integration into the superego of the ideals for which the war is supposed to be fought. In some persons the fear of induction represents a fear that repressed aggressive impulses may be released.

After induction the ego may be unable to establish new relationships because of a reactivation of old and unsatisfactory attachments to masculine members of the family. Frustration of excessive narcissism may lead to the development of a neurosis.

There are some personality types which fit well into military life. These are persons with a well integrated passive attitude or those in whom a sense of guilt has been satisfied by the subordination of personal activity to higher principles.

Some of the more obvious factors leading to nervous reactions in recruits are monotony, discipline, sexual deprivation, absence from home and the necessity for winning prestige in a new group.

The types of psychopathic reactions which occur vary widely and range from hypochondriasis and psychosomatic conversions to severe psychoses, usually of the paranoid variety.

CHODOFF, Langley Field, Va.

THE EVALUATION OF PROGNOSTIC CRITERIA IN SCHIZOPHRENIA. OTTO KANT, J. Nerv. & Ment. Dis. **100**:598 (Dec.) 1944.

Kant believes that the pessimistic view of some workers concerning the value of prognosis in cases of schizophrenia is unjustified and that when certain limiting conditions are taken into account a rather high degree of predictability can be obtained. The basis for prognostication is the clinical picture and its development. In general, the tendency toward persistence of uniformity of behavior and psychotic symptoms is a benign sign, while every trend toward discordance is a malignant sign because it refers to that basic disintegration of the personality which is the primary result of the schizophrenic process. An exception to this principle occurs when the disorganization is associated with clouding of consciousness, since it is then related to the temporary disturbance of the setting. Clinical structures which can be regarded as benign are (1) those in which clouding and confusion are persistent; (2) those in which the more schizophrenic-like symptoms, such as paranoid ideas and hallucinations, are centered around primary

changes in the emotional sphere of either a manic or a depressive character; (3) those in which alternating states of excitement and stupor are associated with fragmentation of mental activity provided that some of the characteristics of the malignant conditions which remain on a uniform psychologic level are not present.

Of malignant import are all other conditions characterized by the predominance of "direct process symptoms," the latter term including both changes of behavior in the direction of disorganization, dulling and autism of gradual and insidious development, and the subjective perception on the part of the patient of a loss of normal feeling of personality activity and related experiences of foreign influence applied to mind or body.

A prognostic indicator which may prove of value is the interview with the patient under the influence of sodium amytal. A schizophrenic disorganization which at least temporarily disappears under the action of the drug is less fixed than one which is resistant to the medication.

An acute type of onset, a prepsychotic extraverted personality, pyknic body build and the presence of definite precipitating factors are indicative of a favorable prognosis.

The author emphasizes that the value of prognostication is dependent on the accuracy of evaluation of the prognostic factors. Individual symptoms must be considered in relation to the entire picture. CHODOFF, Langley Field, Va.

THE DUTY PROBLEM OF THE PSYCHIATRIC CASUALTY: A RAPID METHOD OF DECISION. ROBERT S. SCHWAB, War Med. **6**:144 (Sept.) 1944.

Schwab presents a simple neuropsychiatric evaluation sheet, which consists of a graph easily made out, to be attached to the psychiatric casualty's record, so that his condition and his prognosis can be understood at a glance. The graph has four variables: A. The amount of stress experienced by the patient, whether long hours of hard work in a tropical climate, intense danger under shelling and bombing, unusual responsibility, bad news from home or combinations of more than one factor. B. The degree or amount of the breakdown—including loss of ability to do work; loss of appetite, weight or sleep; fatigue; somatic symptoms; crying; amnesia; conversion symptoms, and any other significant facts. C. The amount of previous instability—abnormal personality traits; nervous breakdown; chronic illness; poor work, school or sex adjustments; bed wetting; overdependence on parents, and other inadequacies. D. The amount or degree of recovery or comeback after the stress has been removed by admission to the sick list and the start of therapy.

Analysis of the cases of men who fully recovered showed that their graph $\frac{A \times D}{B \times C}$ was greater than 1. For those who retained their symptoms in spite of two months of therapy, the rate was less than 1. PEARSON, Philadelphia.

Meninges and Blood Vessels

MENINGITIS DUE TO POST-TRAUMATIC CEREBROSPINAL RHINORRHEA. MILO C. SCHROEDER, Arch. Otolaryng. **40**:206 (Sept.) 1944.

The most common cause of cerebrospinal rhinorrhea is trauma resulting in comminuted fracture. Other etiologic possibilities are (*a*) damage during an operation, (*b*) necrosis caused by pressure of a tumor or hydrocephalus, and (*c*) congenital anomalies. The bony defect may be found in the posterior wall of the frontal sinus, in the cribriform plate of the ethmoid bone or in the walls of the sphenoid sinus. The prognosis of cerebrospinal rhinorrhea is poor. Sooner or later meningitis develops.

Schroeder reports 2 cases of meningitis secondary to cerebrospinal rhinorrhea. In the first case a tumor of the cerebellopontile angle was removed through an

opening made in the skull behind the ear. Shortly after the operation the patient complained of a clear, salty fluid dripping from his nose. One month later meningitis developed, the predominating organism being the staphylococcus. In the second case cerebrospinal rhinorrhea developed two days after the patient had fractured his nose and face in a motor accident. On the third day after the accident unmistakable signs of meningitis were present. The offending organism was the pneumococcus. In both cases recovery followed heroic doses of sulfadiazine, adequate water intake and, in the second case, antipneumococcus serum, administered intravenously.

RYAN, Philadelphia.

PREVENTION, TREATMENT AND END RESULTS OF MENINGITIS. N. SILVERTHORNE, Canad. M. A. J. **52**:252 (March) 1945.

Silverthorne reviews 166 cases of influenzal meningitis and 271 cases of meningococcic infection (all bacteriologically proved) which were observed at the Hospital for Sick Children in Toronto between 1919 and 1944. The use of sulfonamide compounds has been the most important method of treatment in shortening the course and reducing the fatality. Influenzal meningitis has been sporadic in its occurrence. Meningococcic infections were sporadic until 1939, but from 1940 to 1943 there was an increase in the incidence of cases of this infection. Bacteriologically, 70 of the 71 spinal fluid strains examined from patients with influenzal meningitis have been of type B. Meningococcic infections during a sporadic occurrence of the disease have usually been caused by strains of type II. During an increase in the incidence of this infection in 1941 and 1942 there was a decided increase in the occurrence of strains of group I. Most patients with influenzal meningitis followed after recovery have been normal mentally and physically. All patients with meningococcic infection treated with sulfonamide compounds or with serum and sulfonamide compounds have been normal on discharge from the hospital.

J. A. M. A.

Diseases of the Brain

POST-TRAUMATIC EPILEPSY. WILDER PENFIELD, Am. J. Psychiat. **100**:750 (May) 1944.

Penfield states that epileptic seizures may be produced by many types of injury to the brain. A closed injury seldom produces seizures, but when it does the injury usually produces a contusion, with subsequent scar formation. Subdural hematoma seldom produces chronic seizures except in the presence of a meningocerebral scar. With head injuries, penetration of the dura and laceration of the brain greatly increase the likelihood of seizures. Healed abscess of the brain results in a high incidence of chronic seizures. Simple meningitis seldom causes habitual seizures except when it results from thrombosis of cortical vessels, with subsequent scar formation. Cortical thrombophlebitis due to other factors is probably a frequent cause of habitual seizures. Epilepsy seldom follows cerebral embolism or thrombosis. Simple hydrocephalus rarely, if ever, produces chronic seizures. The types of focal cerebral injury here detailed may produce a focus of abnormal spontaneous neuronal discharge. Penfield, from his own observations, sees no importance in the inheritance of a tendency to fits. The focus of neuronal hyperirritability is not in the scar but in the adjacent cortex, usually a small marginal gyrus which has partially atrophied but contains functioning neurons. The vascular supply of such neurons is insufficient for constant adequate oxygenation. Therefore, in the surgical treatment of acute trauma any gyrus that is partially destroyed should be removed. In the surgical excision of epileptogenic scars such marginal partially atrophied gyri must also be removed.

FORSTER, Philadelphia.

INTRACRANIAL SUPPURATION SECONDARY TO DISEASE OF THE NASAL SEPTUM. LLOYD K. ROSENVOLD, Arch. Otolaryng. **40**:1 (July) 1944.

Of the primary conditions that result in intracranial extension of infection, abscess of the nasal septum and submucous resection of the septum are probably the most common. Rosenvold reports 58 collected cases of intracranial suppuration secondary to septal disease. Though the incidence of complications is low, the mortality is high. There may be invasions of the intracranial space by adjacent, or regional, pathways and by distant, or indirect, pathways. The regional, or direct, extension comprises invasion (1) through traumatic dehiscences, (2) through natural bony passages, (3) through bony dehiscences consequent to osteomyelitis, (4) through veins by retrograde thrombophlebitis and (5) by way of the perineural sheaths of the olfactory nerves. The distant, or indirect, pathways are represented by (1) the general circulatory system (septic pathway) and (2) neighboring organs, with intermediate infection as a result of septal disease, e. g., otitis media following submucous resection. Extension to the intradural structures by way of the peripheral lymphatics probably does not occur. The author's experiments with rabbits seem to favor a vascular (thrombophlebitic) type of spread from the nasal septum to the intradural contents.

Of the various intracranial conditions consequent to disease of the nasal septum, purulent meningitis is by far the most common. Thrombosis of the cavernous sinus is next in order. Extradural and subdural abscess probably represent direct extension by osteitis or osteomyelitis. Abscess of the brain is rare.

Careful preoperative study is important in preventing complications following operation on the nose. Postoperative packing or splinting is a much disputed subject. Some surgeons never pack the nasal chambers after submucous resection, while others splint the septal flaps tightly. Tight and prolonged packing predisposes in many cases to postoperative suppurative complications by preventing free drainage. On the other hand, poor splinting may permit free bleeding, and the resulting blood clot may easily suppurate. The author believes that packing should never be left in the nose for more than twenty-four hours after an operation on the septum.

Acute tonsillitis following submucous resection is a complication that may favor intracranial extension of suppuration and should not be regarded lightly. The exact mechanism of extension in those cases in which otitis does not develop as an intermediate infection is not clear. To prevent tonsillitis, it is well not to keep the nose tightly packed for a long time. In cases in which both tonsillectomy and submucous resection are indicated, the former operation should precede the latter by several weeks.

RYAN, Philadelphia.

MÉNIÈRE'S SYNDROME. RESULTS OF TREATMENT WITH NICOTINIC ACID IN THE VASOCONSTRICTOR GROUP. MILES ATKINSON, Arch. Otolaryng. **40**:101 (Aug.) 1944.

Atkinson states that in cases of idiopathic Ménière syndrome one of two vascular mechanisms is at work. There may be a primary vasodilator or a primary vasoconstrictor mechanism, either of which can produce the characteristic picture. The two groups of cases can be differentiated by means of the intradermal test with histamine. Accurate grouping is extremely important because the treatment appropriate in one group is not only inappropriate but actually harmful in the other.

The series reported comprises 110 cases, in which treatment was given for the vasoconstrictor type of Ménière's disease over a three and one-half year period. Nicotinic acid was found to be the best drug for vasodilation. Its action is at the periphery of the vascular system, on the smallest vessels, as is evidenced by the cutaneous flush which follows its administration. This distal response is just the effect desired, since it is the circulation in the capillaries of the stria vascularis which is thought to be at fault, at least as far as aural manifestations are con-

cerned. It is essential to use nicotinic acid, and not nicotinamide. While the two drugs are interchangeable as regards their vitamin effect, they are not interchangeable as regards their vasodilator effect. Nicotinamide has no vasodilator action. The method of treatment found most efficacious has been to start with injections, intravenous or intramuscular, and then, after a period which depends on the response to treatment, gradually to wean the patient from injections to oral medication only. In this series of cases, in which treatment was exclusively with nicotinic acid, the vertigo was either relieved or greatly modified in 84 per cent.

RYAN, Philadelphia.

THE NATURE OF TRANSIENT OUTBURSTS IN THE ELECTROENCEPHALOGRAM OF EPILEPTICS. DENIS WILLIAMS, Brain **67**:10, 1944.

Williams states that the electroencephalogram of epileptic patients during seizures is always abnormal, while the interseizure records may be either normal or abnormal. When abnormal, the record may be nonspecific, but an episode seizure discharge may be superimposed. Williams investigated the relation between the appearance of episodic discharges in the electroencephalogram and the liability of the patient to epileptic attacks. A patient who had had one definite and one questionable grand mal seizure was found to have spontaneous larval petit mal discharges. It was found that closure of the eyes produced similar electrical disturbances. During alterations in the p_H and the gas tension of the blood the reflex disturbances behaved in the same way as to spontaneous wave and spike formations. The efficiency of the trigger mechanism, closure of the eyes, was not affected. Williams concluded that in this instance even the smallest paroxysmal outburst represented abnormal cerebral activity of an epileptic nature. The electroencephalograms of epileptic patients, normal controls, neurotic persons and patients with head injuries were studied and classified as normal or abnormal, and the abnormal records were further classified as (*a*) not specifically epileptic, (*b*) containing larval epileptic outbursts or (*c*) containing other paroxysmal outbursts. Larval epileptic outbursts included high voltage, abnormal waves with sudden onset and cessation, conforming to the described types of organized patterns. Other paroxysmal outbursts included all other types of transitory disturbances, such as are usually associated with epilepsy but are not well enough defined to be considered larval epileptic attacks. Williams found that abnormal electroencephalograms were six times as common in epileptic patients as in normal controls; larval epileptic disturbances occurred in more than 25 per cent of epileptic patients but did not occur in nonepileptic subjects; paroxysmal outbursts, both larval and others, occurred in 56 per cent of epileptic patients but in only 0.5 per cent of nonepileptic subjects, and paroxysmal outbursts occurred thirty times as frequently in patients with head injuries as in nonepileptic subjects and were more common after penetrating wounds.

Williams studied a group of patients with states frequently associated with epilepsy. This group was divided into patients with a constitutional and patients with a symptomatic epileptic tendency. Patients with a constitutional epileptic tendency included (*a*) twins both of whom presented paroxysms of wave and spike activity in their electroencephalograms, but only one of them had clinical seizures, and (*b*) a patient whose only seizure resulted from the oral administration of a small dose of camphor and who presented in his record paroxysmal disturbances suggestive of epilepsy. These disturbances were still present three and a half months after the administration of camphor and hence were considered indicative of a convulsive tendency.

Patients with a symptomatic epileptic tendency included (*a*) persons with paroxysmal outbursts without overt seizure (a patient with glioma of the right hemisphere, a patient with bilateral atrophy of the frontal lobe, a patient with osteomyelitis of the occipital bone and 3 patients with head injury) and (*b*) patients with paroxysmal outbursts following open or closed head injury and subsequently followed by overt seizures.

From these results, Williams concludes that the presence in the electroencephalogram of paroxysmal disturbances in an epileptic patient or in one suspected of having epilepsy can be confidently considered as supporting evidence for the diagnosis of epilepsy. Nonspecific and nonepisodic changes cannot be so construed. The presence of paroxysmal changes in the electroencephalogram in cases of known cerebral disease, for example, neurosyphilis, should not be considered as an argument against the validity of using the presence of such outbursts as confirmatory evidence of epilepsy when epilepsy is suspected but, instead, should be considered as evidence of a serious liability of the patient with cerebral disease to the development of epilepsy. Thus, the old clinical concept of latent and active epilepsy is supported by the correlation of clinical and electroencephalographic data.

FORSTER, Philadelphia.

ACCIDENTAL HEAD INJURIES: PROGNOSIS IN SERVICE PATIENTS. C. P. SYMONDS and W. RITCHIE RUSSELL, Lancet **1**:7 (Jan. 2) 1943.

This paper is concerned with a series of 242 service men with a variety of injuries to the head due to accidents which may also occur in civilian life, in contrast to head injuries sustained in actual warfare. The injuries are classified as "acute," signifying that the patients were admitted to the hospital within three weeks of the accident.

It is pointed out that post-traumatic amnesia ends when the patient is able to give a clear and consecutive account of the events around him. This lucidity must be continuous, and not punctuated by episodes of amnesia. A source of frequent error is the assumption that because a patient is aware of what is happening around him he will be able to recall these events later. Determination of the true end point of amnesia requires continuous, close observation. The duration of post-traumatic amnesia may be taken as an index of the severity of the injury only with limitations, namely, that it does not take into account the degree of local injury.

Comparison of the prognosis with the duration of the post-traumatic amnesia reveals that as the latter becomes longer the prognosis becomes worse. There is a rise in the proportion of deaths when the amnesia exceeds one day, and a further significant rise when it lasts over seven days. Of the group with the longer duration of amnesia, only one third returned to duty successfully. Among 193 of the patients who returned to duty, it was found that the incidence of relapse was not higher in those who had been treated for a relatively short period.

The study reveals that the prognosis is usually good. About 80 per cent of patients who survive the acute stage return to duty (usually heavy) within a few months. This figure is comparable to that pertinent to head injuries received in civilian life.

A résumé of treatment follows: All patients were nursed in bed until they were free from symptoms and were then encouraged to get up and increase their activities gradually. The rate of progress was judged by the symptoms. Lumbar puncture was done in all cases but those of the mildest injury to ascertain the cerebrospinal fluid pressure and the presence or absence of blood. Puncture was repeated if the pressure was high (over 250 mm. of water), if there was much blood or a considerable degree of pleocytosis and if the tap relieved headache or restlessness. Sufficient fluids were given to quench thirst. No restriction was placed on posture in bed. Sedatives were used as little as possible to avoid prolongation of mental confusion. Persistent moderate confusion was not considered a contraindication to the patient's being up provided he appeared none the worse for it. At times, naturally apprehensive patients were encouraged toward greater activity in spite of symptoms. Activity was not allowed to progress until headache, restlessness and excessive fatigue appeared. Gradually increasing activity was determined by the individual case.

Comparison of patients with acute injuries and a much larger group with chronic injuries (patients admitted more than three weeks after injury because

of unsatisfactory progress) reveals that the percentage of men returned to duty but invalided later was much higher in the latter group. The percentage of men finally invalided who had post-traumatic amnesia of over seven days was about the same for the group with acute injuries and for the group with chronic injuries. However, when the period of post-traumatic amnesia was shorter, the incidence of patients who were finally invalided was much higher in the group with chronic injuries. This indicates the presence of factors other than duration of post-traumatic amnesia which affect prognosis.

Symonds suggests that the mental constitution before injury plays an important part in the prognosis; hence, the predisposition to mental disorder was investigated in this series and was found to be more than twice as common in the group with chronic disorders. The investigation was based on the personal history, with respect to backwardness or failure to reach average standards at school; history of any functional nervous illness requiring medical care or absence from work; a poor work record, i. e., failure to hold a job longer than six months, or a family history of alcoholism, marked eccentricity, mental illness or nervous breakdown requiring medical care in the parents, sibs or blood relatives, such as uncles, aunts or step-siblings.

Comparison of the histories of all patients (acute and chronic) with evidence of this predisposition and the histories of patients who showed no such predisposition reveals that the percentage of the men finally invalided was nearly twice as high in the "predisposed" group.

Of 111 men with head injuries in the flying personnel of the Royal Air Force, only 13 (12 per cent) were invalided. These men had all been primarily selected by the air crew selection board as having a sound mental constitution. Of 844 men other than flying personnel, 405 (48 per cent) were finally invalided. Twenty (18 per cent) of the Royal Air Force group had a personal or family history of mental instability, as compared with 325 (38 per cent) of the group of 844 nonflying personnel. This relatively poor prognosis is not to be explained by less severe injury, as measured by the duration of post-traumatic amnesia; to the authors a relatively good mental constitution seems the most probable explanation of the difference.

SANDERS, Philadelphia.

CHRONIC SOLID SUBDURAL HEMATOMA. R. A. MONEY, M. J. Australia **1**:224 (March 3) 1945.

According to Money, solid subdural hematoma is rare. A man aged 23 presented symptoms suggestive of the presence of a cerebellar tumor on the left side. Preparations were begun for an exploratory suboccipital operation. As a preliminary step, burr holes were made in the skull over both occipital lobes. On the left side the dura mater was thick and discolored; and when it was cut through brown fluid and old liquid blood escaped, indicating the presence of an old subdural hematoma. About an ounce (30 cc.) of liquid was evacuated by lavage and suction, with immediate relief of symptoms, and a small piece of corrugated rubber was inserted in a forward direction. It was hoped that the remainder of the hematoma would drain out this way. After the discovery of the hematoma, the patient recollected that about the end of March 1942, while playing soccer, he had received a blow or kick on the head, which knocked him down. He continued the game for at least half an hour in a dazed condition; yet this minor injury must have been sufficient to tear one of the cerebral veins entering the sagittal sinus and start bleeding into the subdural space. Later the patient had a generalized epileptic seizure; the headaches persisted and papilledema increased. These, and other, observations made it obvious that a large, probably clotted and organized subdural hematoma was still present. After a large osteoplastic flap had been raised and the thickened dura reflected, a substance having the appearance of liver was encountered in all directions. This liver-like mass represented a solid subdural hematoma. The patient made a good recovery.

J. A. M. A.

Diseases of the Spinal Cord

SECOND ATTACK OF POLIOMYELITIS AFTER THIRTEEN YEARS. J. WYLLIE, Canad. J. Pub. Health **36**:156 (April) 1945.

A woman at the age of 32, in October 1942, had a second attack of poliomyelitis, having had a first attack thirteen years previously, at the age of 18. The first attack, which had developed after intimate contact with a sister who had a paralytic attack of poliomyelitis, had left the patient with wasting and flabbiness of the calf muscles of the right leg but with little loss of function. The patient walked with a slight limp. During the second attack, examination revealed a partial paralysis of both legs and weakness of the lumbar muscles. Wyllie reports that treatment with the Kenny packs was begun on the day of her admission to the hospital and was continued daily for twenty-five days. On her discharge there were some loss of power in the extensor muscles of the right thigh and loss of power in the muscles of the left thigh, but improvement in the muscles of the lumbar region.

J. A. M. A.

DELAYED PARAPLEGIA FOLLOWING FRACTURES OF VERTEBRAE. L. ROGERS; Brit. J. Surg. **32**:514 (April) 1945.

Rogers says that when paraplegia complicates a vertebral fracture it is usually a concomitant condition produced at once. Rarely is the onset of paraplegia delayed. He cites cases in which there was an interval between the injury to the back and the onset of paraplegia. A seaman aged 22 was blown up by a torpedo explosion, walked to the ship's side, clambered overboard, swam away from the ship and then became paraplegic. A member of the air force injured in a Spitfire crash experienced pain between the shoulders but no other symptoms. Paraplegia developed in forty-eight hours. Another patient had a cycling accident. He walked a mile, then sat down because of pain in the back and was unable to rise because of paraplegia. A girl of 17 was in a bicycle collision with a car. She picked herself up, was taken by car to the doctor's house and walked inside. She then experienced numbness and paralysis. In 2 of the described cases the paraplegia was transient, resolving completely in a few days' time. In the other 2 cases it was persistent, and exploration was carried out, with improvement in both cases following the removal of bony encroachment on the spinal canal. In the cases of transient paralysis delayed paraplegia is probably due either to subpial hemorrhage or to edema, which, when fully established at a varying interval after the injury, is sufficient to impair conduction in the cord. With absorption of the effusion in some twenty-four to forty-eight hours, or even longer, conduction is once more restored. Persistent delayed paraplegia is an indication for operation and removal of the bone block produced by displacement of the vertebral fragments.

J. A. M. A.

POLIOMYELITIS OF PSEUDOMYOPATHIC FORM. M. GESTEIRA, Pediat. e puericult., Bahia **13**:117 (March-June) 1944.

According to Gesteira, poliomyelitis of the pseudomyopathic type is characterized by sudden appearance of paralysis either after an infectious period typical for poliomyelitis or without such a period. Two or more members of the family become simultaneously ill, an occurrence which is rare with poliomyelitis. Early paralysis and consequent moderate atrophy are symmetric and are regularly distributed in the proximal areas of the limbs, near the pelvic and scapulohumeral joints. There is lordosis. The type of gait and posture is similar to that of myopathy. The hands become clawed or show a tendency to this deformity. In cases reported by the author the electrodiagnostic examination late in the course of the disease failed to show any reaction of degeneration, an observation which suggests complete regression of paralysis.

J. A. M. A.

CERVICAL DISK PROLAPSE. B. BROAGER, Acta psychiat. et neurol. **19**:45, 1944.

In 5 of 285 cases of prolapse of an intervertebral disk the involved disk was in the cervical region: In 3 cases it was the sixth cervical intravertebral disk, in 1 case the fifth and in 1 case the fourth. Four of the patients were men, between the ages of 33 and 50, and 1 was a woman, aged 46. The history revealed traumatic injury to the spinal cord in 3 of the 5 cases. Pain was the most common initial symptom. In only 1 case was there quadriplegia; in 2 cases there were unilateral radicular paresis and atrophy, with inferior paraparesis in 1 of them; in 1 case there was inferior paraparesis only, and in 1 neurologic signs were normal. The Brown-Séquard syndrome was present in 1 case. Sphincter disturbances were present in 1 case. Roentgenographic examination revealed narrowing of the involved intravertebral space in 3 cases; in all 5 cases typical spondylosis deformans with osteophytes was demonstrated in the cervical portion of the spine, most pronounced at the level of the ruptured disk. Myelograms taken with iodized oil showed nothing characteristic of prolapse of the disk. A partial block was found in 2 cases and a total block in 2. The three distinct syndromes described by Stookey as typical of prolapse of the cervical disk may be useful if the differential diagnosis between a small prolapse of a cervical disk and intrinsic disease of the cord is difficult. But if the prolapse is large, the syndromes of Stookey will not be of any help in the differential diagnosis of intraspinal tumor and prolapse of a disk. The history of a specific traumatic injury to the cervical region of the spine combined with signs of an intraspinal tumor in this region should be suggestive of prolapse of a cervical disk. These symptoms, combined with roentgenographic signs of localized spondylosis deformans of the cervical region of the spine, especially narrowing of an intravertebral space, would also point to prolapse of the disk.

J. A. M. A.

Society Transactions

ILLINOIS PSYCHIATRIC SOCIETY

David Slight, M.B., *President, in the Chair*

Regular Meeting, April 5, 1945

A Power Factor (P) in General Intelligence: Effects of Lesions of the Brain. DR. WARD C. HALSTEAD, Chicago.

On the basis of work with patients with cerebral and other types of injury, with normal subjects and with infrahuman animals during the past ten years, I have formulated a set of behavioral indicators which have been validated biologically. An exploratory factor analysis was made of data relating to these indicators secured from 50 neuropsychiatric patients. The factor patterns were found to separate or to come together in biologically and clinically meaningful ways. One factor thus isolated has been identified as a kinetic power (P) factor. It is altered by injury to the brain, fatigue and anoxia and in certain psychiatric states (Halstead, W.: *J. Psychol.* **20**:57-64, 1945; *Science* **101**:615-616 [June 15] 1945).

During the early formative stages of personality in the growing child, it is probable that the power factor (P) operates to a greater or less extent as an antineurotic factor. In the normal adult its presence in adequate strength is a necessary protection against neurotic resolution of conflict. When the P factor is reduced by excessive physiologic stresses of military combat, for example, the consequence for the normal adult is the "combat neurosis," so commonly observed in the recent war.

Whether the P factor is similar to or identical with the concept of vigilance described clinically by Head as lowered in aphasic patients is not yet clear. While similarities are already suggested, direct comparison is hampered by Head's failure to specify quantitative indexes for the measurement of vigilance. More promising, however, is the prospect for comparison of the P factor with the general factor found by Lashley to be altered in proportion to the mass of lesions induced in the cortex of the rodent brain. Data on a diversified series of adequately studied patients, with histologic verification of their neural lesions, are necessary before this comparison can be made. My associates and I are slowly accumulating such data in our laboratory.

DISCUSSION

DR. W. S. MCCULLOCH, Chicago: I am happy to see a psychologic test that bears a rather fruitful relation to physiologic, or even anatomic, alterations. There are behind this short presentation so many kinds of data and so much of each kind that the simple conclusion, as the author stated it, can scarcely carry the weight that it should. The fascinating thing to me, a mere neurophysiologist, is this: The one effect to be expected from anoxia, the use of barbiturates, an inadequate blood sugar level or reduced temperature is a lowered metabolic rate of the nerve cells. Under such a condition the nerve cells would not be able to produce their normal potential in a normal length of time. It follows that if one tried to drive such nerve cells at high speed they would quickly fatigue, they would cease to respond. This would be detected most easily in the brain waves, which should be slow, and in the sensorium, which should be clouded, or in any demand for alternating performance, such as the flicker or the tapping test, or perhaps in the field of attention (I am not sure but that the problem of attention can be reduced to the same principle). At least this factor, of a physiologic nature,

is obviously an ingredient in the kinetic power of intelligence as it has been presented, for it is related to the repeated activity of nerve cells in the same way.

The second condition that might easily underlie any diminution in the power factor is a lack of impulses coming in from other parts of the nervous system; and that would mean in general that, while plenty of attention might be left to handle a simple problem, there would scarcely be enough left for the whole peripheral field. There are within the central nervous system many reverberating circuits, which yield a background of excitation for the rest of the neural activity. Probably the largest single mass of such circuits runs through the frontal pole. Therefore, any large cortical injury, especially frontal lobotomy, by interrupting some of these circuits, should leave the patient with a fairly normal intelligence quotient but with inability to push through, probably a narrowing of the field of awareness spatially, and possibly temporally; the result should be social ineffectiveness. Thus, this second factor, of an anatomic nature, is to be expected as an ingredient of the power factor, for it also contributes to the repeated activity of nerve cells.

I like particularly the term "power factor," for it implies just what it should —a rate of doing work.

Group Therapy in an Extramural Clinic. DR. KATHARINE W. WRIGHT, Evanston, Ill.

Today, especial interest is being shown in group psychotherapy, owing to the fact that military psychiatrists have found it useful and beneficial. However, this method has other advantages, particularly for patients leaving mental hospitals.

Group therapy meets the need for treatment over a long period; it is consistent with the present psychologic studies, and it helps to desensitize and destigmatize, as well as to socialize, the patient.

The group therapy class at present under discussion is conducted for the purpose of helping hospital patients in their adjustment after return to home life, to teach them about their emotions and to instruct them how better to handle their emotions so as to cope with their present life situation. It is combined dynamics and reeducation.

The method used is as follows: The twenty-six letters of the alphabet are utilized as representative of twenty-six discrete, volitional acts; namely, the acts of writing the respective letters. The very simplicity and uniformity of these acts make them an ideal standard, safely within the usual levels of comprehension. How accurately and well the patient forms the letters is of little moment; it is the manner of his response which is important. This reaction of the patient affords specific diagnostic information to the therapeutist and frequently indicates the psychotherapy to be administered. For example, annoyance is frequently expressed at the extreme simplicity of the task. This usually indicates a concealed feeling of inferiority or inadequacy which troubles the patient. Or self consciousness in varying degrees may be exhibited, thus suggesting emotional instability, such as is based on a sense of insecurity. Sullen resistance to the situation, indicating negativism, is sometimes encountered.

The therapeutist is often afforded the opportunity of administering effective treatment of these reactions on the spot. Usually this can be carried out by means of comments, made to the class and not to the patient, bearing on the nature of the patient's response, the probable causes of his maladjustment and the solution or cure, the parallel being always drawn between the patient's reaction to the test situation and his reaction to the situations presented in life.

This procedure may be varied in several ways: (1) The patients participating may proceed at their own speed and develop a group rhythm; (2) they may follow dictation, which puts them under an authoritative regimen, or (3) they may be confronted with a new situation, such as being asked to write with the left hand. In the first situation, many patients show inability to conform to the group activity and their annoyance at the incident restraint. Rebellion under

authority is a common reaction in the second situation, and in the third situation either fear or a decided relaxation of repression is usual.

Within the last year there was developed the plan of taking notes of the day's proceedings, to be read and discussed at the next class hour. These notes serve as an additional educational tool. Special responsibilities are also assigned to certain members, such as keeping an attendance record and writing notices to absentees.

Statistical evaluations of any type of psychotherapy are difficult to make. However, data were secured with respect to attendance and diagnosis and comments from patients, visitors, doctors and nurses in answer to questionnaires sent out.

The following points were brought out from remarks made by patients: The patient learned to get on with other people; was helped to forget self; gained self confidence; became more independent in making decisions; learned how to relax; became more tolerant; gained an aim in life; learned the value of a goal; learned the difference between emotional reaction and intellectual judgment; enjoyed meeting friends. On the other hand, one woman resented the class after two years' attendance because it reminded her of the hospital. Class attendance was found to be a check on the degree of emotional stability.

It may be noted that most patients give a favorable response. The unfavorable response seems to come, for the most part, from persons with rigid personalities. Some of these persons do admit, however, that the friendly atmosphere in the class assists them to make better social contacts, and this must be considered as of at least some help. Also found in this group are patients who block themselves from help by their intellectual attitudes; nothing so simple could possibly help them. Regular attendance at class has modified this attitude. It is possible to get over to the patient that there is a considerable and important part of himself, other than his intellect, which greatly affects his life and well-being. Intellectual blocking is also found frequently among visitors, both professional and nonprofessional; it is hard for them to join in an emotional experience such as the class provides.

Comments from visitors were mostly favorable, especially from relatives of patients. Some of these visitors mentioned actual help to themselves and noted the benefit to the patients from the friendly atmosphere existing in the class. This bears out the comment of one of the physicians who visited the class, namely, that the important thing accomplished was getting the patients out of their pathetic isolation.

The therapeutic value of group therapy is now recognized by a large number in the psychiatric profession. It is a useful instrument in desensitizing a patient to his mental illness; it may serve to relieve him and his relatives of the stigma of hospitalization in a mental institution, and it affords an outlet for the socialization desperately needed by many neurotic patients and by psychotic patients whose condition has improved.

The studies in this field extending over three years corroborate several statements made by Dr. Paul Federn (Psychoanalysis of Psychoses, *Psychiat. Quarterly* **17**:470 [July] 1943). I agree with him that "it is not astonishing that most psychotics relapse at home or elsewhere when left without continuous support of transference." And, again, "one wins normal transference of the psychotic by sincerity, kindness and understanding."

In conclusion, it may be stated that the group treatment under discussion has met in a practical way the needs of many patients, approximately 240, leaving state hospitals. Not only does it afford the supportive therapy so urgently needed, but the nonverbal technic, a powerful emotional stimulant, provides at the same time a therapy which is both dynamic and educational.

DISCUSSION

DR. CHARLES F. READ, Elgin, Ill.: This interesting communication follows a former article by Drs. Jacobson and Wright (*Psychiat. Quarterly* **16**:944 [Oct.]

1942). Dr. Wright has now applied this technic, as formerly described, to a group in an outpatient clinic. Complete understanding of her paper depends on knowledge of the former presentation, in which the technic was fully described.

This procedure is not a psychologic test in the ordinary sense of the term. It has not been standardized by comparison with the performance of so-called normal subjects. It is evidently a jointly subjective and objective attempt to evaluate the performance of patients observed along the lines she has indicated. As in any psychiatric examination, a great deal depends on the physician's evaluation of the patient in a more or less controlled situation.

For several years I listened to Dr. Jacobson's discussion of this "test" as he developed it, and I must confess that not until I read the article in the *Psychiatric Quarterly* did I appreciate the various implications of the procedure. As described by the authors at that time, and again by Dr. Wright in the present paper, it is evident that psychiatric insight can be obtained in this manner by one who is conversant with the technic—a method which, obviously, should be stereotyped in its application. Evidently, it cannot be picked up and applied offhand by any one and every one, now and then just as one pleases.

As suggested in the first article, many variations are possible if and when they may seem desirable. When one takes into consideration the development of the alphabet used in this procedure, one appreciates the fact that each letter is actually a picture derived through many, many changes during thousands of years. Somatopsychic coordination for the purpose of writing has been conditioned for years in educated persons. This "test" indicates cortical interference with these old patterns by reason of affective disutrbances—disturbances such as occasion misbehavior of various sorts in other fields of neuromuscular activity.

It would be interesting, of course, to carry out this procedure under the hypnotic suggestion of such emotions as fear and hostility. Within its limitation, it parallels the psychic drama. In fact, the patient operating in this situation may well be described as enacting on a small stage a drama, with the psychiatrist standing by, not only as observer but as a participant in the play. The latter is accepted by the subject as a manifestation of his superego, as well as an aggravator of the handicapping forces with which he has to deal.

Doubtless, much of the good effect of this therapy results from group discussions, so well described by Dr. Wr'ght. The A B C's, used as described, seem to furnish an excellent basis for psychiatric guidance en masse, provided one can employ the technic with finesse.

CHICAGO NEUROLOGICAL SOCIETY

Ralph C. Hamill, M.D., *President, in the Chair*

Regular Meeting, April 10, 1945

Diastematomyelia: Report of a Case. Dr. Paul C. Bucy and Dr. Harry P. Maxwell.

Diastematomyelia is a congenital separation of the lateral halves of the spinal cord.

A 9 month old child with a congenital dermal sinus at the level of the third lumbar vertebra was operated on for removal of the sinus, and an anomalous bony structure was found. Exploration revealed two separate spinal cords enclosed in one dura mater above the third lumbar vertebra and each cord descending caudally in its own dura mater below this level. The bony anomaly proved to be a spur projecting posteriorly from the body of the third lumbar vertebra and separating the two duras. At the age of 26 months neurologic examination revealed

a generally normal condition, with no gross evidence of spinal or cerebral dysfunction.

A discussion of the literature included the summary of a review, in 1940, by Herrin and Edwards and a description of the anomaly studied in cross section, demonstrated in 1940 by Lichtenstein ("Spinal Dysraphism": Spina Bifida and Myelodysplasia, ARCH. NEUROL. & PSYCHIAT. **44**:792 [Oct.] 1940).

DISCUSSION

DR. A. EARL WALKER: I have seen 1 case of this anomaly (*Am. J. Roentgenol.* **6**:571-582, 1944). In that case there was a dilatation of the spinal canal at the site of diastematomyelia. An operation was performed because I suspected a congenital tumor at that point, rather than splitting of the spinal cord. I wonder whether there was such a dilatation in the case presented here.

DR. R. P. MACKAY: May I ask where the surgeon found the conus terminalis, and how much of the cord existed below the spur of bone?

DR. PAUL C. BUCY: We did not explore far enough down to find the conus; it extended into the lower lumbar part of the canal at least. There was considerable anomaly of bone here; the spur shown in the drawing was not the only defect. There was no spinous process at this level, and an anomalous development of the laminas existed. There was, however, no definite enlargement of the spinal canal. Roentgenographic visualization of the bony structure is not satisfactory in a child of this age. I could not say that there was no dilatation at all, but none was detected.

Angiomatous Malformation of the Sylvian Aqueduct with Remarks on Management of Aqueductal Obstructions. DR. CARL GRAF.

This paper was published in full in the January 1946 issue of the *Journal of Neuropathology and Experimental Neurology*, page 43.

Connections of the Cingulum. DR. WENDELL J. S. KRIEG.

The cingulum has long been known to exist in man and the mammals generally. It is usually considered to carry associational fibers of the medial, or cingular, cortex, and in man such connections certainly predominate. Experimental lesions of the thalamus and cortex of the rat, however, demand a different interpretation of the cingulum.

Fibers from the anterior nuclei of the thalamus enter the anterior thalamic peduncle and run as far forward as the rostral end of the caudate nucleus and then turn dorsally, perforating the corpus callosum, and form the rostral end of the cingulum. Fibers reaching it at successively more caudal levels are piled on laterally. Meanwhile, some fibers turn into the medial cortex. There is a strong tendency for the axons to continue in the cingulum until they reach the caudomedial angle of the cortex, where they bend somewhat laterally and curve under the posterior forceps of the corpus callosum. Here they terminate in the cortex of the retrosplenial region.

The cingulum also receives representations from the ventrolateral thalamic nuclei. These axons pass nearly directly laterally and dorsally and fall in place on the lateral aspect of the cingulum at a more caudal level than those of the anterior thalamic nuclei. They do not show so strong a tendency to continue to the retrosplenial region but drop off along the way, both to the dorsal and to the medial cortex.

The cingulum also receives representations from the cortex itself. Each cortical lesion was shown to contribute to the bundle and its lateral extension by trails of granules, which became successively more oblique in the more caudal levels. Many of these fibers do not reach the cingulum proper but, rather, enter a laminar lateral extension of it, immediately under the cortex.

When reconstructed from the dorsal aspect, the cingulum and its accompanying lamina form a subcortical layer of regularly arranged, uncrossing fibers, which converge to the retrosplenial region. There are no other accumulations of asso-

ciational fibers. The direction of conduction seems to be exclusively caudomedial, not the reverse.

Hence, in the rat the retrosplenial region is regarded as an important thalamic and cortical associational area. A corollary of this is the principle that points in the cortex associate with other points caudomedially placed.

DISCUSSION

DR. G. VON BONIN: This paper is extremely valuable and has cleared up many points that were ambiguous. The retrosplenial region is divided into a number of areas—26 and 29 are the most important. It is not of the ordinary neocortical type. However, in higher forms, as in primates, these areas shrink to insignificance and lie largely in the depth of the sulcus corporis callosi. In our experiments on monkeys and chimpanzees, my associates and I have been able to establish connections passing from this retrosplenial area to the anterior nucleus of the thalamus. We have not been able to find in monkeys any corticocortical connections; that does not mean that they do not exist. They may not be massive enough to show up with the method we used; it may also be that the area is too small for the electrodes.

Dr. Krieg expressed doubt about the olfactory character of the hippocampus. In view of the work of Fox and Magoun, I feel that the hippocampus should not be considered olfactory. In an article in the ARCHIVES on the emotional mechanism, Papez proposed the association of the hippocampus with the anterior nucleus of the thalamus and the mamillary body. I should like to ask Dr. Krieg whether, on the basis of his experience, he has any comment on this concept.

DR. WENDELL J. S. KRIEG: Papez' ideas on the cingulum are very stimulating. I do not know what I believe, except that it is the chief associational tract in the lower forms. But it has been thrown into the limelight recently by the work of Freeman and his group, in Washington, D. C., who say that in frontal lobectomy they can cut anything they like but that when they section the cingulum there are personality changes.

I purposely hedged in my statements about this retrosplenial region, because I have not made the architectural study of the rat which I think is necessary. At least, for my own purposes I want to know where the areas are. It is certain that several areas in this region are much larger in the lower forms than in man. There are other parts of the retrosplenial group which are strongly connected with the corpus callosum. Thus, a major associational area is present here, but in higher forms I believe the emphasis has been shifted; perhaps it is the familiar situation of "paleo" and "neo" in associational mechanisms.

The Mesodermal Tissue in Nerve Lesions and Repair. DR. FREDERICK HILLER.

In one series of many hundreds of experiments on cats, the sciatic nerve was cut and sutured with black silk, or autogenous and homogenous grafts were employed to bridge gaps of 2 to 5 cm. In another series, cats were shot through the thigh, and either nerve contusions resulted without interruption of the anatomic continuity of the nerve or the nerve was shattered. Repair was effected in this group by end to end sutures or by grafts. Histologic examination of all these nerves, by combining the Bodian and the Van Gieson stain, has revealed the importance of the reactions of the mesodermal tissue in the repair of nerve injuries.

Milder forms of nerve contusion, like other forms of mechanical nerve trauma and so-called neuritis, lead to disintegration of the myelin sheaths with or without destruction of the axis-cylinders. The original structure of the endoneurial tubes remains unaltered, and the nerve fibers regenerate within their old endoneurial sheaths. The nerve fascicles retain their isomorphous structure, although the mesodermal endoneurium may react to the trauma with a localized cellular, and

later fibrous, hyperplasia, leading to some endoneurial fibrosis. The restitution of neural function is good and requires a short time.

More severe traumatic lesions of the nerve damage the mesodermal endoneurium as well. A histiocytic and fibroblastic proliferation ensues, which interrupts the continuity of the endoneurial tubes. As the mesodermal cells and fibers transgress the limits, the original endoneurium, the Schwann cells and the regenerating nerve fibers follow them. There are a profuse branching off, intermingling and confusion of young nerve fibers in the area of regeneration in such a traumatized nerve, and the isomorphous nerve structure is changed into a heteromorphous one.

When the trauma affects the border of the perineurium and the nerve fascicle proper, a mesodermal and ectodermal response follows, analogous to the reaction just described. As proliferating mesodermal elements of the endoneurium establish contact with the proliferating histiocytes and fibroblasts of the perineurium and epineurium, Schwann cells with regenerating nerve fibers leave the nerve fascicle and proceed between lamellas of collagenous fibers of the mesodermal perineural membranes. They will grow in this new environment as far as the reactive mesodermal proliferation may attract Schwann cells.

The same guiding function of proliferating mesodermal cells in nerve regeneration is seen in every process of nerve repair. The ends of a divided nerve show the various stages of nerve trauma, increasing in severity toward the cut surface. Because of the caudal progress of neurotization, the relation of proliferating mesodermal endoneurial cells to Schwann cells and nerve fibers is more obvious in the central than in the distal segment. There is a gradual transition from isomorphous neurotization within intact endoneurial tubes, about 5 mm. cephalad to the cut surface, to a more heteromorphous neurotization in the traumatized end of the central segment. The more gently a nerve is severed, the less will be the traumatic disorganization of the endoneurial tubes by mesodermal proliferation and the less the heteromorphous disarrangement of regenerating nerve fibers. When a nerve is not cut, but is severed by the shattering, bruising and tearing effect of a bullet, severe structural changes with heteromorphous neurotization within the fascicle and what may be called a herniation of ectodermal nerve tissue into the perineurium and epineurium are found several centimeters centrad to the nerve end. In the suture line itself, regeneration of nerve fibers by outgrowth of naked axons is negligible. The two ends are held together by mesodermal fibers, which assume in time the characteristics of collagenous connective tissue. It is along these fine mesodermal fibers, which can be stained for collagen a few days after injury, that the regeneration of nerve fibers in relation to proliferating Schwann cells gets under way. Schwann cells proliferate by themselves into the semiliquid medium of the nerve gap, but the main regeneration of fibers follows the scaffolding of the fibroblasts and their collagenous fibers. Strands of fibrin may act as guiding elements, but it seems most probable that here, again, the proliferation of mesodermal cells and fibers precedes the neurotization proper. Proliferating mesodermal cells and fibers, as well as Schwann cells originating from the distal segment, meet those from the central segment in the gap. Whatever the shape and direction of the mesodermal tissue elements between the separated nerve ends happens to be, it is this scaffolding which determines the course of the outgrowing nerve fibers into the degenerated distal segment. There is no need to assume that some sort of obscure chemotropism directs regenerating nerve fibers. The presence of such a hypothetic force is easily disproved by the usual deviation of regenerating nerve fibers which follow the proliferating fibroblasts of the hyperplastic perineurium and epineurium in the suture line. Nerve fibers accompanied with Schwann cells follow the proliferating mesodermal cells deep between the adherent muscle fibers, and a certain number almost regularly turn backward into the proliferative epineurium of the central segment and downward into the mesodermal sheaths of the distal segment. These fibers are lost to the ultimate functional regeneration.

In these experiments, a delayed end to end nerve suture—sixty days after the nerve was sectioned—produced a heteromorphous nerve structure over a greater distance and seemed to favor the undesirable deviation of regenerating nerve fibers into the excessively proliferative perineurium and epineurium of the central and distal segments.

The study of nerve grafts affords a further illustration of this concept of neurotization. One has only to exchange the effect of a nerve trauma for that of a tissue necrosis to see that the process of neurotization remains practically the same. A freshly planted autogenous graft may heal, with the mesodermal endoneurial cells surviving this operation. The effect will be an isomorphous neurotization within the original endoneurial tubes, even though the habitual necrosis of the original Schwann cells results in a sort of *Abbau* of the decomposition products of the myelin sheaths and axis-cylinders, different from a wallerian degeneration. In an ideal case an autogenous graft may become neurotized, much like the degenerated distal segment of a sharply severed nerve.

Such ideal results are the exception with autogenous grafts and are never seen with homogenous grafts. Here, the neurotization is preceded by a mesodermal organization of the partly necrotic graft tissue. The original endoneurial membranes serve as a scaffolding for the proliferative mesodermal cells and seem to guarantee the maintenance of the direction of the mesodermal and, later, the nerve fibers. Yet the proliferation of the mesodermal cells and fibers is excessive, and far from being limited to the original endoneurial membranes. Wherever these membranes have succumbed to the general tissue necrosis, the mesodermal organization will become retarded and increasingly irregular. Finally, the mesodermal organization may include the perineurium and will then obliterate the anatomic and functional barrier between the perineurium and the nerve fascicle proper. The epineurium shows a conspicuous mesodermal proliferation. It is this kind of proliferative mesodermal organization which decides the neurotization of many autogenous and of all homogenous grafts. These grafts show a quantitatively good supply of regenerated nerve fibers, but their structure is heteromorphous, with an enormous amount of nerve fibers situated in many fine bundles between the dense collagenous fiber strands of the perineurium and epineurium. The nerve fascicles reveal an intense endoneurial fibrosis. One may say that the structure of a homogenous graft corresponds essentially to the neuromatous aspect of a severely traumatized nerve but appears to be more favorable than that of a suture line.

Our studies indicate that the use of dead tissue grafts or of grafts preserved in alcohol or other fixatives shows nothing but disadvantages. The necessary mesodermal organization is rendered much more difficult, and the irregularity of the final tissue structure is so great that a large percentage of regenerating nerve fibers never reach the distal nerve segment.

Nerve grafts in gunshot wounds show principally the same reaction as grafts used to repair a sharply sectioned nerve. There is frequently a more excessive mesodermal proliferation of the epineurium, with epineurial neurotization of the graft, depending on the interval after injury at which the transplantation has been performed. The often difficult mesodermal organization of grafts requires considerable more time for the functional regeneration of a nerve than does an end to end suture. The final effect may suffer from extensive, thorough necrosis of the graft, as well as from the intense fibrosis within the graft.

DISCUSSION

Dr. George B. Hassin: In 1907 Perroncito, a brilliant student of problems of nerve degeneration and regeneration, gave in one of his contributions 700 references—probably more, as I got tired counting them. Since then the number of contributions has increased considerably, and, as Dr. Hiller has shown in his exceptionally good demonstration, the interest in this subject is still alive. I can touch only on some points brought out by Dr. Hiller, by showing five lantern

slides. My experience with the pathology of nerve injuries is based on the study of 32 cases from Spielmeyer's collection of 180 cases, all from World War I. The nerves from each case had been sectioned and stained with four methods and thus were ready for investigative work. In addition, I studied the rich experimental material of Nageotte (Paris) and Ranson.

It seems that the behavior of the mesodermal tissue in nerve degeneration and regeneration depends on the type and the severity of the injury. With mild forms, when the nerve fiber has been cut, the myelin, axon and adjacent membrane and cells of Schwann degenerate below the place of injury and, as a diagram of Hjelt's (1860) shows, only the endoneurial, mesodermal membrane remains in the peripheral stump. Into the empty tubes formed by the parallel rows of the endoneurial cells grow new nerve fibers from the central stump. Hjelt assumed that the preserved endoneurial cells become transformed into nerve fibers. Such a view is, of course, inadmissible, as mesodermal tissue cannot be transformed into nerve fibers. Thirty-one years after Hjelt's publication, Büngner described in the peripheral stump parallel rows of fibers and nuclei known as cell *cordons* of Büngner, who stated that they consisted of cells of Schwann. The cells became, he thought, "neurotized"; that is, they were transformed into nerve fibers and fused with the central stump, and thus a regenerated nerve fiber was formed. Büngner's conclusions, like those of Hjelt, were not based on facts, as his cell *cordons* are not formations of Schwann cells but rows of endoneurial cells, to which Dr. Hiller has repeatedly called our attention.

The behavior of the mesodermal tissue is different with severe injuries, such as lacerations of nerve fibers. The proliferation of the connective tissue fibers is not in the form of isomorphous strands, as Dr. Hiller called them, but of irregularly scattered masses, forming scars, which prevent any possibility of nerve regeneration. With a third type—mild contusion or concussion—there is no mesodermal reaction whatever, both the parenchyma and mesodermal tissue undergoing necrosis. On the whole, the results of Dr. Hiller's excellent experimental studies (on cats) wholly coincide with observations on human subjects, demonstrating the great importance of the mesodermal tissue in injuries of the peripheral nerves, in the processes of their degeneration and regeneration.

Dr. Frederick Hiller: I wish to emphasize the point that in my opinion the different nerve elements react as a unit, in degeneration and in regeneration. The proliferation of the endoneurial, mesodermal elements is an essential part in nerve regeneration and determines the character of nerve regeneration, particularly in cases of nerve injuries. My studies on many hundreds of different nerve injuries and nerve grafts have shown how the neurotization of nerve sutures, of nerve contusions and of various grafts follows the pattern of primary mesodermal organization. The observations, as demonstrated in the pictures shown here, could never have been made by examining human material only. I feel that the role of the mesodermal tissue in nerve regeneration has been neglected heretofore and that new concepts have been developed which will lead to a better understanding of this process.

Book Reviews

Intelligence and Its Deviations. By Mandel Sherman, M.D., Ph.D. Pp. 286, with illustrations, glossary and index. New York: The Ronald Press Company, 1945.

In the first sentence of his preface the author states that "the purpose of this work is to present theoretical, experimental and clinical material on intelligence and its deviations. The subject is presented in such a way that it may be used in courses in departments of psychology and medicine." He proceeds to do this by gathering together in one volume of fifteen chapters the material usually found in books on general, social and abnormal psychology. The orientation is primarily that of the academic psychologist and the physician. There is considerable discussion of theoretic questions, such as a definition of intelligence, mental growth and the relation of environment and intelligence. There is some mention of less frequently recognized, but nevertheless important, problems connected with the measurement of intelligence. Thus, the question of motivation is touched on, as well as the difficulty of establishing a zero point in the measurement of intelligence and the frequently found disparity between intelligence and the level of the adjustment. On the whole, however, the author adheres to the more usual aspects of intelligence and intelligence testing. The facts are stated in simple fashion and are often supported with experimental data.

The weakness of the book, and it is a serious one, lies in the fact that the author makes no mention of the new approaches in intelligence testing. He still lays most of his emphasis on problems of mental classification and questions of deficiency, at least four chapters being devoted to various aspects of mental deficiency. While this discussion may be of value to the medical student, mentioned in the preface, it does not merit so much importance in a book on intelligence, especially when newer and more important aspects of intelligence testing are neglected. The psychologist who administers the intelligence test has long moved on from the approach which concerned itself primarily with mental level alone. Nowhere in the book is mention made of the psychologic research which evaluates the deviations in mental functioning in order to obtain an objective personality picture, a measure of mental deterioration and, in some instances, a diagnosis of mental disease. Rather, the author says that it is difficult to define the "exact mental level of a psychotic patient because the raw score on a test cannot give information as to the deteriorative process." Although he points out that certain failings are likely to occur with certain types of mental illness, he does not recognize the value of such clues but, rather, brands the tests as inadequate. In general the book must be considered relatively superficial and as adding little to the understanding of intelligence and its deviations.

An Introduction to Physical Anthropology. By M. F. Ashley Montagu, Associate Professor of Anatomy, Hahnemann Medical College, Philadelphia. Price, $4. Pp. 326. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

This book is an excellent introduction to a complex and controversial field of scientific investigation. The author presents his material in a clear, concise manner, and without bias. It is intended for the general reader rather than for the specialist and covers a great deal of ground.

In a brief introduction, the author defines the scope of physical anthropology. He then describes seriatim the zoologic classification of the primates and discusses the factual basis for the theory of man's origin and evolution from an anthropoid progenitor. Considerable space is devoted to an analysis of the divisions and ethnic groups of man, with emphasis on the difficulties encountered by anthropologists in

developing sound criteria for classification. The last part of the book deals with the subtle relationships of culture, mind and body and the much disputed question of the relative importance of heredity and environment on man's development. At the close of each chapter there is a selected list for further reading. The accepted methods of measurements in physical anthropology are listed and described in the appendix. The index is unusually complete and contains numerous cross references.

Prof. Ashley Montagu, in agreement with most eminent anthropologists, is a firm believer in the fundamental spiritual and biologic equality of all mankind. Throughout the book he intersperses pithy comments, supported by scientific facts, on the absurdity of the concept of "race and blood superiority" and points out that "cultural isolates" do not represent genetically discrete "races," as is often assumed by the uninformed layman. An interesting section of the book reviews the evidence that the physical characteristics of a "pure race" actually change when the group is transplanted to a new physical environment.

Of particular interest to students, scientists and educators, this book is highly recommended as instructive and interesting reading.

Examining for Aphasia: A Manual for the Examination of Aphasia and Related Disturbances. By Jon Eisenson. Pp. 28, with 4 pages of illustrations. New York: Psychological Corporation, 1946.

This manual has been compiled by a clinical psychologist and speech pathologist and is intended for the use of speech pathologists in planning a program of language rehabilitation for individual aphasic patients. The manual presents a comprehensive language examination in a clear form and should be useful for recording the progress in language function. The instructions for the various test items are specific and easily followed, and much of the test material is included in the manual.

The author states that his interest is in speech therapy, and not in neurologic and neurosurgical implications of language dysfunctions; consequently, it is not a criticism of his work to point out that the examination is not entirely satisfactory for use by the clinical neurologist.